Clinicopathologic Conference

Rhabdomyolysis and Pancytopenia in a Young Man

Discussants

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PETER BARNES, MD:* A 26-year-old Hispanic man was brought to the Los Angeles County-University of Southern California (LAC-USC) Medical Center by family members because of an acute change in his mental state. He was well until eight days earlier, when he first noted weakness, malaise, fever and chills. Over the next few days, myalgias, a sore throat, nausea and vomiting developed. During the three days before admission, his symptoms worsened and he became increasingly lethargic, with episodes of confusion and fecal incontinence. No seizures were witnessed. The patient had no previous health problems, took no medications and had no allergies. There was no history of alcohol, tobacco or illicit drug use. Born in El Salvador, he had worked in a textile factory until he came to the United States six months before admission. He was presently unemployed.

On physical examination he appeared well developed, well nourished and in considerable respiratory distress, having shaking chills. The blood pressure was 120/80 mm of mercury, the pulse 124 beats per minute, respiratory rate 44 and temperature 39.1°C (102.4°F). He had bilateral conjunctival injection and scleral icterus. The mucous membranes were extremely dry. His neck was supple and there were no abnormalities on cardiac examination. Rales were heard and dullness to percussion noted at the right base. There was minimal abdominal tenderness diffusely, without peritoneal signs. No masses or organomegaly was noted, bowel sounds were normoactive and the stool was positive for occult blood. He was oriented to person and place only and babbled incoherently at times. He was somnolent but arousable, and there were no focal neurologic signs.

A right basilar infiltrate was seen on the chest x-ray film. The hemoglobin was 12.6 grams per dl, the mean corpuscular volume 88 cu microns. The leukocyte count was 2,900 per μl with 78% segmented neutrophils, 6% band forms, 10% lymphocytes and 6% monocytes. The platelet count was 19,000 per μl and the reticulocyte count 0.2%. The peripheral blood smear showed mild anisocytosis and poikilocytosis, occasional burr cells and rare fragments. The platelet morphology was normal.

Serum electrolyte values were as follows: sodium 132, potassium 2.8, chloride 100 and bicarbonate 16 mEq per liter. Other serum values were as follows: calcium 6.8, phosphate 5.4, blood urea nitrogen (BUN) 124 and creatinine 5.6 mg per dl; total protein and albumin were 6.6 and 2.9 grams per dl, respectively; total bilirubin was 5.0 mg per dl, with a direct fraction of 2.3 mg per dl; alkaline phosphatase 226 units per liter (normal less than 110), creatine phosphokinase (CPK) 20,360 units per liter, lactic dehydrogenase (LDH) 6,390 units per liter, alanine aminotransferase 580 units per liter and aspartate aminotransferase 2,360 units per liter.

A urinalysis showed a specific gravity of 1.012, 1+ protein and 4+ blood. The sediment contained three to five erythrocytes per high-power field. The urinary sodium level was 74 mEq per dl. An arterial blood gas analysis with the patient breathing room air disclosed a pH of 7.46, oxygen pressure of 79 torr, carbon dioxide pressure of 23 torr and bicarbonate of 16 mEq per liter. A Gram's stain of a sputum specimen showed 3+ leukocytes and no organisms.

The patient was given saline and 20 mg of furosemide intravenously in the emergency room. A lumbar puncture was done with some difficulty, yielding bloody fluid. The first tube contained 179,000 erythrocytes and 17 leukocytes, 16 of which were mononuclear cells. The fourth tube showed

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ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
CPK = creatine phosphokinase
LAC-USC = Los Angeles County-University of Southern California
LDH = lactic dehydrogenase

54,000 erythrocytes and no leukocytes. The protein was 210 mg per dl and the glucose 47 mg per dl, with a simultaneous serum glucose level of 118 mg per dl. A Gram's stain and an india ink preparation of the cerebrospinal fluid specimen were negative, and no acid-fast bacilli were seen. The cryptococcal antigen was negative. A regimen of ampicillin sodium and gentamicin sulfate was started intravenously for a presumed bacterial infection of uncertain source.

Several hours after admission, a nasotracheal tube was inserted because the patient's respiratory rate persisted at 45 to 50 per minute. Several sputum smears were negative for acid-fast bacilli. Tests for hepatitis B surface antigen, ameba antibody and blood and urine toxins were negative. There were no fecal leukocytes and a thick blood smear showed no malarial parasites. The prothrombin time, partial thromboplastin time and thrombin time were abnormally prolonged but corrected when normal plasma was added in a 50:50 ratio. The protamine sulfate test was negative.

Over the next 48 hours, the patient's temperature continued to be as high as 39.4°C (103°F). His blood pressure remained normal and he did not have oliguria. Because of heavy sedation, his mental state could not be readily evaluated. With intravenous hydration, the hemoglobin fell to 10.2 grams per dl and the BUN and creatinine levels to 98 and 4.0 mg per dl, respectively. The leukocyte count fell to 2,000 per μl with 57% segmented neutrophils and 18% band forms. The platelet count was 17,000 per μl. The chest film showed an increasing infiltrate in the right lower lobe, with fluid in the minor fissure. On the third hospital day, a diagnostic laboratory test result was received.

Dr Goldstein will discuss the differential diagnosis in this case.

Differential Diagnosis

DAVID A. GOLDSTEIN, MD:* This patient presented with several problems, including renal insufficiency, pancytopenia with hemolysis and a possible clotting defect, pneumonia, mental state changes, gastrointestinal disturbance and abnormal results on liver tests. I believe that these and some of his other problems are manifestations of an overwhelming infection, and I hope to discuss each of these problems in an attempt to reach a diagnosis.

The renal insufficiency in this patient can be characterized as acute renal failure. This was manifested by myalgias, 4+ hematuria with few red cells on microscopic urinalysis, a BUN value of 124 mg per dl and a CPK level of 20,000 units per liter. The elevated CPK level and abnormal findings on a urinalysis strongly suggest that rhabdomyolysis is the cause of the acute renal failure. There are many causes of rhabdomyolysis. The high fever and the pronounced shift to the left in the leukocyte count suggest an active infection in this previously healthy patient.

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I would like to review the infectious causes of rhabdomyolysis (Table 1). There is no clinical evidence of gas gangrene or tetanus. Leptospirosis is an important possibility that I will discuss below. Influenza, myxoma and Coxsackie viruses also cause rhabdomyolysis but should not cause severe multisystem disease in a normal host. The pneumonia is described as lobar and this, too, mediates against a viral infection. Shigellosis has been reported to cause rhabdomyolysis but does not often result in multisystem involvement, which was clearly present in this case. In addition, no bloody diarrhea or fecal leukocytes were noted. There is one report of a case of rhabdomyolysis from *Herbicola lathyri* contamination of hyperalimentation fluid, but this is not applicable to our patient. Reye's syndrome is a disease of children characterized by severe liver failure and increased intracranial pressure. It does not appear to be present in this case.

While I do believe this patient had bacteremia, he was never in septic shock, and we cannot invoke hypotension as a cause of the rhabdomyolysis. Finally, *Pseudomonas* bacteremia, leptospirosis and typhoid fever have been reported to cause rhabdomyolysis. I will discuss these three illnesses below.

This patient had several hematologic abnormalities. There were pancytopenia and hemolysis, manifested by fragmented cells, burr cells, anisocytosis and poikilocytosis. In addition, the patient's prothrombin, partial thromboplastin and thrombin times were prolonged. The negative protamine sulfate test makes disseminated intravascular coagulation extremely unlikely. This patient's abnormalities corrected on administering a 50:50 dilution of normal plasma, suggesting a clotting factor deficiency state and not the presence of an inhibitor, as might be seen in autoimmune disorders. The hematologic features suggest a microangiopathic hemolytic anemia. While many disorders can cause this problem (Table 2), a severe infection seems the most likely possibility.

The evidence for pneumonia in this patient included the dullness and rales on physical examination and a right basilar infiltrate on a chest film. In addition, there were hypoxemia

TABLE 1.—*Infectious Causes of Rhabdomyolysis*

Gas gangrene	Reye's syndrome
Tetanus	Septic shock
Leptospirosis	Myxoma virus
Viral influenza	*Pseudomonas* bacteremia
Coxsackie virus infection	Typhoid fever
Herbicola lathyri bacteremia	

TABLE 2.—*Causes of Microangiopathic Hemolytic Anemia*

Malfunctioning values or vascular prostheses
Disseminated carcinomatosis
Scleroderma
Malignant hypertension
Postpartum renal failure
Thrombotic thrombocytopenia purpura
Lupus erythematosus
Periarteritis nodosa
Vasculitis
Transplant rejection
Hemolytic uremic syndrome
Septicemia

and a respiratory alkalosis. While no bacteria were seen on a sputum Gram's stain, the clinical features suggest infectious lobar pneumonia. The most common cause of lobar pneumonia in hospital inpatients is, of course, the pneumococcus. This patient's mental state changes lead us also to consider the possibility of an aspiration pneumonia.

The mental state changes in this patient are somewhat enigmatic. He was confused, lethargic, disoriented, babbling and somnolent. The lumbar puncture seemed to be a traumatic tap, and there was a normal computed tomographic scan. Based on this information, I believe the mental state changes were due to a metabolic encephalopathy. An analysis of the chemistry findings shows evidence of acute renal failure, hypoxemia and bacteremia as possible causes of the changes in his mental state.

Rhabdomyolysis, acute renal failure and microangiopathic hemolytic anemia are important aspects of this patient's illness. Let us discuss a few conditions that might explain this presentation. Scleroderma, malignant hypertension and postpartum renal failure can be excluded on the basis of the history and examination. Thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome are considerations. The hemolytic-uremic syndrome is seen predominantly in children. Thrombocytopenia, microangiopathic hemolytic anemia and progressive renal failure are characteristic. This patient, however, did not have hypertension, there was no generalized bleeding and there was no purpura. The patient did have a fluctuating mental state, but there was no hepatosplenomegaly and he did not have a palpable, tender kidney. For these reasons, I am reluctant to diagnose the hemolytic-uremic syndrome in this case. Thrombotic thrombocytopenic purpura is also a possibility in this patient. He did have thrombocytopenia, anemia, fluctuating neurologic signs and a fever but did not have generalized purpura. In addition, patients with thrombocytopenic purpura rarely have severe renal failure, although they do have mild to moderate renal insufficiency.

Finally, I would like to mention five infectious disorders that deserve strong consideration as causes of this patient's illness. When I first read this case through, I was sure that the diagnosis was leptospirosis. This disorder is rarely diagnosed in southern California, however. It is most common in the tropics, and there have been several cases reported in Texas in which rhabdomyolysis has occurred. Leptospirosis occurs when people are exposed to the urine of animals infected with *Leptospira*. The manifestations of this illness that fit so nicely in this patient are fever, chills, myalgias—which can lead to clinically unmistakable rhabdomyolysis—nausea, vomiting and conjunctival suffusion. Leptospirosis may cause severe liver, kidney and central nervous system disease. The aminotransferase levels may be elevated, but less so than in viral hepatitis. The leukocyte count can be normal, elevated or depressed. Hemolytic anemia has been reported, and disseminated intravascular coagulation has been seen. Gastrointestinal hemorrhage can occur and could explain our patient's *o*-toluidine (Hematest)-positive stools. In addition, a hemorrhagic pneumonia can develop in these patients. In summary then, other than the fact that this patient should not contract leptospirosis in California, it is a thought-provoking possibility. The diagnosis of leptospirosis requires early suspicion and laboratory confirmation by agglutination titers.

A second diagnosis that needs to be mentioned is legionnaire's disease, which can present with headache, nausea, myalgias and a cough. The sputum can be inflammatory but less purulent than in pneumococcal pneumonia. Diarrhea is present 30% to 50% of the time. There may be confusion, lethargy, delirium and depression. In addition, there is often a relative bradycardia, which was not present in this patient's case. Legionnaire's disease is a possibility, although in a previously healthy young man, it is somewhat unlikely. In addition, the multiplicity and severity of the patient's problems make me lean away from legionnaire's disease.

Still another possibility is *Pseudomonas* bacteremia. This can present with a full-blown picture of septicemia, with many of the manifestations of this patient's illness. *Pseudomonas* certainly causes pneumonia, which might indeed require intubation. It also is a cause of rhabdomyolysis. But why should this patient contract a *Pseudomonas* infection? Serious *Pseudomonas* infections occur in hospitalized patients, usually with severe burns, infected wound sites or decubitus ulcers. Intravenous drug users and patients on respirators can also contract this disease. As a rule, we do not see otherwise healthy persons out of hospital present with a *Pseudomonas* infection.

Another important diagnostic possibility is malaria. One must consider malaria as a possible cause of fever and hemolytic anemia in a Hispanic patient. The diagnosis can be made by examining a thick blood smear, which was negative in this case.

Diagnosis—Typhoid Fever

I believe this patient was suffering from typhoid fever. There are two common modes of presentation of *Salmonella typhi* infections. First, a patient may have enterocolitis manifested by nausea, vomiting, colicky abdominal pain and diarrhea. Typhoid fever, however, may present as an overwhelming multisystem disorder, as in this patient. Patients may have headaches, cough and diffuse abdominal pain. Hepatitis and bone marrow suppression are common. Splenomegaly and a relative bradycardia are also characteristic. The lack of these two features is a little troubling but, in one series of 975 patients, relative bradycardia was seen in only 30% to 40% of the cases.[1] Rose spots are also a well-known manifestation of typhoid fever. These are usually seen in the first one to two weeks, but in only 10% to 15% of cases. What troubled me about the diagnosis is the fact that rhabdomyolysis is not usually considered to be a manifestation of typhoid fever. However, I was able to find a report of one such case.[2] The diagnosis of typhoid fever can be made in the first one to two weeks of the clinical illness by blood cultures. These will be positive in 90% of cases and the organisms grow within 24 to 36 hours. In summary, then, I believe this patient had a fulminant case of typhoid fever and that the diagnostic test was a blood culture positive for *Salmonella typhi*.

DR BARNES: Blood cultures from admission grew *Salmonella typhi*, sensitive to ampicillin. Salmonella group D and group E titers were positive at 1:320, and the typhoid H titer was 1:80. A haptoglobin level four days after admission was less than 5 mg per dl (normal 27 to 139), confirming the presence of hemolysis.

The patient did well and the nasotracheal tube was removed on the eighth hospital day. By this time, the BUN and

creatinine levels had fallen to 56 and 2.7 mg per dl, respectively. The CPK, LDH, bilirubin and transaminase levels gradually fell to normal.

On the 11th hospital day, the patient passed large quantities of bright red blood and melanotic stool per rectum. His hematocrit fell to 17%, and high-output cardiac failure developed, requiring insertion of an endotracheal tube and Swan-Ganz catheterization. He was given transfusions and vigorous diuresis and responded very well to therapy. He had no further complications and was discharged four weeks after admission.

In summary, this patient experienced many common complications of typhoid fever, such as pancytopenia, delirium, hepatitis and gastrointestinal bleeding. He was also unfortunate enough to have several rare manifestations of the disease: hemolysis, rhabdomyolysis and acute renal failure. To my knowledge, there were no cases reported in which all of the above complications were noted in the same patient.

I have asked Dr Overturf, who has a great deal of experience with typhoid fever, to discuss the complications of this unusual disease.

Complications

GARY D. OVERTURF, MD:* Infection due to *Salmonella typhi*, or enteric fever due to other *Salmonella* serotypes, characteristically produces a stepwise increase in the fever over two to three days, followed by sustained fever in the range of 38.9°C to 40°C. This usually follows an incubation period of 10 to 30 days (median, 15 days). The early symptoms of typhoid are those of a systemic bacteremia, and the complications of this phase are those that might accompany any other Gram-negative bacteremia. Other than anorexia, gastrointestinal signs are not prominent during this time. During the second week of illness, patients characteristically have signs and symptoms referable to the abdominal involvement with the typhoid bacillus, primarily of the Peyer's patches in the distal ileum. Intermittent episodes of sparse diarrhea may occur, interspersed with intervals of no stools whatsoever. Fever, malaise and myalgia may continue. Near the end of the second week, a complication may develop, such as intestinal perforation or gastrointestinal hemorrhage. Often this complication occurs when patients have begun to defervesce and their condition is improving.

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TABLE 3.—*Signs, Symptoms and Physical Findings in 126 Patients With Typhoid Fever at Los Angeles County-University of Southern California Medical Center*

Symptoms and Physical Findings	Patients	
	Number	Percent
Symptoms		
Constitutional symptoms		
Fever	114	90
Malaise	82	65
Headache	56	44
Chills	38	30
Enteric or abdominal symptoms		
Diarrhea	88	70
Nausea or vomiting	84	67
Abdominal pain	76	60
Anorexia	55	44
Right lower quadrant pain	4	3
Right upper quadrant pain	2	2
Other		
Cough	37	29
Delirium	15	12
Pleuritic pain	2	2
Physical Findings		
Temperature ≤37.7°C (99.9°F)	6	5
37.8°C to 38.8°C (100°F to 101.9°F)	17	13
38.9°C to 39.9°C (102°F to 103.9°F)	63	50
≥40°C (104°F)	40	32
Relative bradycardia	49	39
Hepatomegaly	24	19
Splenomegaly	20	16
Combined organ enlargement	19	15
Rose spots	13	10

In Table 3 are outlined the symptoms and physical findings among 126 patients with typhoid fever at the LAC-USC Medical Center seen from 1969 to 1977. Fever is the single most common constitutional symptom, occurring in nearly 90% of the patients. Malaise, myalgia or both are next in frequency; headache occurs in nearly half of the patients. Chills and sweats may also be present.

Enteric symptoms usually occur during the second week of the illness. The young man presented here had only been ill for eight days, so enteric symptoms were minimal. Nausea and vomiting are nearly as likely to occur as diarrhea, and the diarrhea rarely produces significant hypovolemia. Abdominal pain is particularly prominent toward the end of the second week. Anorexia may be more common than is noted in Table 3 because the symptom is not spontaneously elicited by physicians. Right lower quadrant pain usually indicates a severe ileitis, and right upper quadrant pain suggests significant biliary complications during the acute stage. These latter patients often have physical signs and liver test abnormalities consistent with acute cholecystitis.

The respiratory tract is frequently involved during the first week in patients with typhoid. Nearly a third of the patients have a cough and about 1% have pleuritic pain. Pharyngeal discomfort or mild upper respiratory tract symptoms may also occur. Up to 10% of the patients, particularly adults, may have delirium of some degree. Clinically unmistakable encephalopathy may occur in a smaller number, and young children may have febrile seizures. In developing countries, clear-cut meningitis occurs at times.

The physical findings in typhoid mirror the reticuloendothelial involvement of the disease. Nearly all patients are febrile, and 80% have a fever in excess of 38.9°C, which is often sustained. Hepatomegaly or splenomegaly (or both) may occur in 20% to 25% of patients, but it is more frequently noted in the very young. Rose spots, a classical sign of typhoid fever, are appreciated infrequently by modern physicians (10% of cases). Typically, they occur during the end of the first week.

Another classical symptom, relative bradycardia, was noted in only 31% of our patients, but much more frequently in adults. In children, the relationship between the normally rapid pulse and fever is not easily discernible as relative bradycardia. In adults, this finding may be present in 60% of cases.

In Table 4 are the associated laboratory abnormalities and clinical complications in 126 typhoid patients. We had never

TABLE 4.—*Associated Laboratory Abnormalities and Clinical Complications in 126 Typhoid Patients*

Laboratory	*No. Abnormal/No. Measured*	*Percent*
Hematology		
Leukocyte count ≤ 5,000/μl	77/126	61
Hemoglobin ≤ 9.9 grams/dl	49/126	39
Platelets ≤ 50,000/μl	43/126	34
Pancytopenia	38/126	30
Chemistry		
Bilirubin ≥ 2.0 mg/dl	4/83	5
ALT or AST ≥ 60 units/liter	74/96	77
Complications		
Gastrointestinal hemorrhage*	13	10
Encephalopathy	4	3
Cholecystitis, acute	3	2
Ileal perforation	2	2
Renal failure, acute	2	2
Bone/soft tissue infection	2	2
Amnionitis	1	1
Relapses	6	5
Death	1	1

ALT = alanine aminotransferase, AST = aspartate aminotransferase

*Occult hemorrhage occurred in an additional 15 of 126 (12%) patients.

observed a patient with rhabdomyolysis before this case. Involvement of the hematopoietic system is nearly universal. Classically, the leukocyte count in cases of systemic salmonellosis is said to decline. This, however, was seen at some time during the hospital stay in only 60% of the patients. In contrast, leukocytosis of greater than 10,000 per μl was extremely unusual unless intestinal perforation occurred. Similarly, mild to moderate anemia is frequent and severe anemia (hemoglobin of 9.9 grams per dl or less) was seen in 38% of the patients. Thrombocytopenia of moderate severity also occurred in about a third of the cases. Pancytopenia was noted in 30%.

A variety of electrolyte abnormalities may occur, depending on the degree of diarrhea, nausea and vomiting. Nearly all episodes of renal failure in typhoid fever are due to prerenal factors. Disseminated intravascular coagulation and acute tubular necrosis may also account for some cases.

Hyperbilirubinemia in cases of typhoid is distinctly unusual, and of the four patients cited in Table 4 with bilirubin levels higher than 2.0 mg per dl, three had symptoms of biliary obstruction or pyogenic gallbladder disease. In two episodes, this prompted a biliary surgical procedure. The patient under discussion may have had biliary obstruction or cholecystitis with spontaneous resolution, and hyperbilirubinemia may have been in part due to a brisk hemolysis. Transaminase levels are frequently elevated in patients with typhoid fever. Three fourths of our patients had abnormal values, the mean elevation being 100 to 150 units per liter, although values as high as 5,000 units per liter were noted. Such elevations may be seen in other conditions mimicking typhoid fever, such as brucellosis, malaria and amebiasis.

Gastrointestinal hemorrhage is the most frequent complication of typhoid fever, occurring in 10% of our patients. All required fluid resuscitation or transfusion. Occult hemorrhage occurred in an additional 12%. Ileal perforation is the most life-threatening complication in typhoid and occurred in 2% of our patients. The incidence of gastrointestinal hemorrhage and ileal perforation has not changed significantly since the use of antimicrobial agents. This may be due to the fact that, on the average, patients came to the hospital after eight to nine days of fever. It is possible that, with earlier diagnosis and prompt institution of antibiotic therapy, these complications would decline. However, survival following these complications has been greatly enhanced by improved supportive measures, and death is now unusual in modern hospitals.

Relapse remains a problem with typhoid fever, occurring in 5% to 7% of patients over the past 20 years. Before the use of antibiotics, relapse rates were as high as 20% to 25%. In our own series of 29 patients treated with chloramphenicol (mean dosage 65 mg per kg of body weight per day), 6.8% of the patients relapsed and in 96 ampicillin-treated patients, the relapse rate was 4.2% (mean dosage 149 mg per kg per day). Currently we initially use ampicillin given intravenously until defervescence occurs, followed by amoxicillin by mouth to complete a 14-day course.

Typhoid is exclusively a human pathogen, maintained in nature by carriers who unwittingly disseminate the disease. The incidence of carriage increases with age, female sex and coexistent biliary tract disease. In all, 30% of women older than 40 years become carriers, whereas fewer than 1% of children do so. Overall, it is thought that 1% to 2% of all patients with acute typhoid fever become ongoing carriers. In those persons who are identified as new carriers, however, one is rarely able to elicit a history of typhoid fever or exposure to the disease, suggesting that asymptomatic infection and carriage are very common.

REFERENCES

1. Huckstep RL: Typhoid fever, *In* Conn HF, Conn RB (Eds): Current Diagnosis, 6th Ed. Philadelphia, WB Saunders Company, 1980, pp 175-183

2. Rheingold OJ, Greenwald RA, Hayes PJ, et al: Myoglobinuria and renal failure associated with typhoid fever. JAMA 1977; 238:341