Diabetic Ketoacidosis Triggered by Typhoid Fever in a Type II Diabetic

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Diabetic ketoacidosis is a complication that can be precipitated by infection in Type II, as well as Type I, diabetics. If an infectious etiology of the ketoacidosis is not actively sought and vigorously treated, a fatal outcome could be erroneously attributed to ketoacidosis rather than the infection. An unusual case of a 43-yearold woman with typhoid fever presenting as diabetic ketoacidosis is reported.

Keywords: Diabetes mellitus, Salmonella typhi, Typhoid fever, Infection, gastroenteral, Ketoacidosis

Infection can lead to ketoacidosis in a Type II diabetic patient who is not normally ketosis-prone. This report is an unusual case of a woman not previously known to have diabetes who was hospitalized for nausea, vomiting, and severe weakness. She was subsequently found to have diabetic ketoacidosis precipitated by typhoid fever.

Case Report

History of current illness. A 43-year-old Filipino woman was semicomatose when admitted to the hospital with nausea, vomiting, and increasing generalized weakness.

Approximately 3 ½ weeks prior to admission, she had become ill in Manila with fever and general malaise. After 2 days she improved and left Manila for a trip to the U.S. via Japan. While in Japan she became weak, dizzy, and nauseated, and had fever and polyuria. She flew to San Francisco a week later. There, she had recurrence of nausea, vomiting, weakness, and polydipsia with intermittent fever and continued polyuria. The weakness progressed over the next 10 days until she could no longer stand or walk without assistance. She was admitted to the hospital with suspected electrolyte imbalance from the nausea and vomiting.

Past history. The patient's family history was positive for adult-onset diabetes in her mother. The patient's personal history was positive for hypertension of 6 years' duration. This had been treated with methyldopa initially, and then acebutolol (Sectral), both of which had been discontinued 1 year before hospitalization. She took no medication on a regular basis.

Physical examination. On physical examination, the patient's temperature was 36.4°C (97.5°F). Her blood pressure was 145/85mmHg, pulse rate was 110 beats per minute, and respiratory rate was 22 breaths per minute with typical Kussmaul breathing. It is unknown whether the patient had orthostasis, because she was severely ill from the time of admission and remained supine during the early hours of therapy.

The patient was obtunded and very weak, with dry mucosa and slightly soft eyeballs. Her skin did not show tenting. Rose spots were not seen in this woman, possibly because she was darkly pigmented and also because the disease had been present for several weeks. Her neck was supple, without adenopathy or thyromegaly. Her back and costo-vertebral angles were nontender. The lungs were clear; the heart had a regular rhythm and a loud grade III over VI harsh systolic murmur. The abdomen was normal. The extremities showed no edema. Peripheral pulses were 2+ and equal. Deep tendon reflexes showed absent knee jerks and questionable left ankle jerk. The Babinski reflex was negative.

Laboratory examination. Initial laboratory values were: glucose 844mg/dL; sodium, 128mmol/L; potassium, 4.0mmol/L; bicarbonate, 3mmol/L; chloride, 98mmol/L; pH, 6.94; Po_2, 18.5k Pa (139mmHg; on room air); Pco_2, 2.5k Pa (19mmHg); creatinine, 2.8mg/dL; acetone, 320mg/dL; and phosphate, 2.9mg/dL. Amylase was not tested. Complete blood count showed 19,400 WBCs/mm^3, with 8% bands.

The chest radiogram showed no active disease. An EKG reading showed borderline sinus tachycardia.

Hospital course. In the first several hours after hospital admission, the patient received IV insulin in increasing doses in the attempt to reduce the ketonemia. She was insulin-resistant and required a total of 774 U of regular insulin in the first 19 hours of hospitalization. She remained on IV insulin until the fourth day, when subcutaneous insulin was begun and the insulin infusion was discontinued.

Alkaline phosphatase, LDH, SGPT, and SGOT showed mild elevations during hospitalization, never more than 150% of upper limits of normal range. Echocardiogram and biliary sonograms were not performed; the patient and her family had requested conservative testing because of financial concerns.

On the day of admission, blood, urine, and stool cultures were ordered. Gentamicin sulfate (120mg loading dose) and ampicillin (2g every 6 hours) were ordered pending the results of blood, urine, and stool cultures.

On the following day, the urine grew moderate Salmonella typhi susceptible to ampicillin (MIC = 2µg/mL) arid trimethoprim/sulfamethoxazole (TMP-SMX) (MIC ≤ 2/38µg/mL) .Coagulase-negative staphylococcus that were susceptible to TMP-SMX (MIC ≤ 0.5/9.5µg/mL) and resistant to penicillin also were cultured. Two blood cultures grew S. typhi susceptible to ampicillin and TMP-SMX.

Gentamicin and ampicillin were discontinued. The patient was begun on TMP-SMX (240mg TMP/1200mg SMX every 8 hours IV for 8 doses, then every 8 hours PO).

Therapy was continued until the sixth day after admission, when a rash developed which appeared to be a drug reaction. Medication was changed to ampicillin (500mg orally every 6 hours) and probenecid (500mg orally every 12 hours). The patient was discharged on the sixth day after admission and appeared to make an uneventful recovery after 20 days of antibiotic therapy.

Follow-up. After the patient's return to Manila, she relapsed. Relapse was documented in the Philippines by a Widal test positive at 1:320 for typhoid H flagella, group D, at all dilutions. It was negative for paratyphoid A, B, and C at levels of trace to 1:80. She was treated with chloramphenicol 4 times daily for 14 days and all titers decreased after treatment. A Widal test performed in 1990 was negative. Subsequent stool cultures after treatment were all negative.

The patient's glucose tolerance improved in the months following discharge from the hospital and she was weaned from insulin therapy. Four-and-one-half months after admission, her blood glucose level was below 100mg/dL fasting and below 18Omg/dL postprandially without pharmacologic (insulin or oral agent) therapy and despite a weight gain of 1.67kg (3 lb). Four years after hospital discharge, the patient remains near euglycemic without medication.

Discussion

Typhoid fever. Typhoid fever is an infrequent cause of morbidity in the U.S., with only about 500 cases reported yearly, 60% of which are imported (the exposure causing infection occurred outside the U .S.). Although typhoid fever is generally an acute systemic disease, it can present with several clinical syndromes including enteric fever, bacteremia, localized infection, or acute gastroenteritis. The average incubation period is 10 days but may range from 3 to 60 days. Because the salmonellae must be phagocytized by cells of the reticuloendothelial system before they begin to multiply intracellularly, patients are initially asymptomatic after exposure, though the bacteria may be found in the bloodstream 24 to 72 hours after exposure. Patients treated with antibiotics prior to ingestion of salmonellae are more likely to manifest the disease, because normal gut flora is somewhat protective. The organisms frequently become concentrated in the gallbladder and are excreted with bile into the intestine, with the stool becoming culture-positive during the third and fourth weeks of the infection.

Typhoid fever usually has an insidious onset presenting with headache, malaise, anorexia, possibly chills, and remittent fever. Abdominal complaints or dry cough may also be present. The frequently described rose spots, which usually occur on the upper abdomen in the second week of the infection, may or may not appear and are frequently difficult to see in dark-skinned people. They occur in less than 50% of cases, and usually fade within hours or days. A strikingly normal pulse rate in the presence of high fever is a typical finding. The fever of typhoid fever ranges from 38.5°C to 40°C. Constipation may be present, or diarrhea may be a

complaint, as may abdominal pain. (1) Hepatosplenomegaly may occur. Delirium or confusional states are the most common neuropsychiatric manifestations of typhoid. However, meningism, convulsions, acute psychosis, myoclonus, and severe myopathy caused by typhoid fever have been reported. (2) When delirium or other severe CNS signs occur, they are often prognostic of a lethal outcome. (3) Diagnosis is usually made from blood cultures, although by the third to fourth week of the disease 75% of stool cultures are positive. Five percent to 10% of cases will have relapse, and 3% of patients will become chronic carriers, with culture-positive stools 1 year after treatment of the infection. This is usually from chronic infection of the gallbladder. The most lethal complication of typhoid fever is intestinal perforation, which may occur unexpectedly during convalescence. Other reported complications include bone and periostial, breast, splenic, and suppurative ovarian cyst abscesses. (4) Optimal therapy is controversial. Ampicillin and chloramphenicol continue to be the most frequently used drugs but TMP-SMX is also frequently used. (5) Currently, ciprofloxacin (Cipro) or ofloxacin (Floxin) would be excellent choices for therapy, but these drugs were not routinely used at the time this patient presented. (6,7)

Extensive reviews of the literature and a computerized medical literature search by the author have been unsuccessful in finding any cases of typhoid fever precipitating diabetic ketoacidosis, although typhoid fever is so common in other parts of the world that perhaps other cases have occurred.

Ketoacidosis. It is common knowledge that any severe infection in a poorly controlled Type II diabetic could induce diabetic ketoacidosis. The author found no reported cases of patients with severe infection and diabetic ketoacidosis who did not subsequently have diabetes. Many Type I diabetics presenting for the first time in diabetic ketoacidosis may have a mild or severe infection appearing to precipitate the acute metabolic deterioration. These patients do not become nondiabetic in the future, although they may have a brief "honeymoon" period during which insulin requirements are extremely low or even zero for a short time.

Drug therapy. In a computerized search of medical literature, the author was also unable to find other case reports of typhoid fever in diabetics. It is therefore unknown whether or not ampicillin therapy leads to an increased relapse rate. A recent reviews (5) of several older studies suggested that inadequate dosage or route of administration of ampicillin could have been responsible for the less favorable results in those studies. The authors of the review article suggested that IV ampicillin in high doses (150 to 200mg/kg/day) is highly effective in treating typhoid fever, results in a more rapid defervescence and a lower relapse rate than chloramphenicol, and is less toxic.

Diabetes and infection. Because it is not known whether the patient's diabetes was controlled prior to developing the infection, or in fact whether or not she was hyperglycemic, since she did not have a prior diagnosis of diabetes, it is difficult to comment whether diabetes predisposed the patient to this infection.

Infection is the most common identifiable cause of ketoacidosis in both adult and pediatric populations. (8) In Type I diabetes, the infections seen may include rare and unusual etiologies as well as the more common ones. Scully and colleagues (9) reported a 14-year-old girl with diabetic ketoacidosis who was subsequently found to have endobronchial mucormycosis in a bronchiectatic abscess. Kennedy and others (10) reported on a 54-year-old insulin-dependent diabetic woman in whom recurrent ketoacidosis was traced to Klebsiella pneumoniae septicemia with emphysematous pyelonephritis.

Infection can also lead to ketosis, hyperosmolar coma, or ketoacidosis in a Type II diabetic who is not ketoacidosis-prone in the basal state. Zakka and Hirose (11) reported a 68year-old diet-controlled diabetic woman who developed Escherichia coli urosepticemia that led to diabetic ketosis.

A 64-year-old man with alcoholism, chronic pancreatitis, cirrhosis, hepatic encephalopathy, and diabetes was reported by Yangco and associates. (l2) The patient presented with hyperosmolar nonketotic coma which had developed following intraarticular steroid injection into the shoulder, and resulted in fatal gas gangrene due to mixed clostridia and E. coli infection of the shoulder.

Although the patient in the present report was later found to have typhoid fever, at the time of admission she was afebrile with nausea and vomiting and had not experienced any rash, cough, chest pain, shortness of breath, abdominal pain, dysuria, or diarrhea in the preceding weeks. The severity of the insulin resistance in this patient strongly suggested an underlying severe infection.

Conclusion

Infection should always be sought as a precipitating cause of diabetic ketoacidosis, even when another obvious cause (omission of insulin therapy) is evident. If cultures had not been ordered and antibiotic coverage not given while results were pending, this patient would very likely have succumbed. The cause of death probably would have been attributed to diabetic ketoacidosis, without typhoid fever ever having been considered.

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