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Case Presentations of the Harvard Affiliated Emergency Medicine Residencies

RECURRENT HYPOGLYCEMIA, HYPOTENSION, AND ALTERED MENTAL STATUS

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Dr Paul Jansson: Today's case is that of a 60-year-old male who presented to the emergency department (ED) for evaluation of hypoglycemia. On the day of presentation, the patient was driving to work and was pulled over by police for erratic driving. While questioning the patient, the police became concerned for an underlying medical reason for the patient's erratic driving and called emergency medical services (EMS).

EMS arrived to find the patient with a room air oxygen saturation of 88%, which improved to 94% with application of supplemental oxygen via a nasal cannula at a rate of 2 L/min. Point-of-care (POC) glucose was measured at 48 mg/dL. An i.v. catheter was placed and 25 g dextrose was administered intravenously while the patient was transported to this hospital, with improvement of his glucose to 109 mg/dL.

On arrival to the hospital, the patient reported feeling "generally unwell" for approximately 2 days prior to his current presentation. Two days earlier, he had noted uncontrollable shivering, a cough, and mild shortness of breath. He had not measured his temperature at home. His symptoms worsened until he felt "dizzy" while driving to work that day. He noted no chest pain or pressure, headache, or abdominal pain, but did endorse chronic lower extremity pain and swelling and decreased urine output for the previous 2 days. He noted no recent travel, sick contacts, or recent illnesses.

Dr David Peak: Could you tell us more about the patient's medical history?

Dr Jansson: The patient reported that he had suffered traumatic injuries from a utility pole accident many years prior, which had left him with chronic neuropathic pain and edema to the lower extremities. He had chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea, for which he used a nocturnal continuous positive airway pressure device. He also reported hypertension, hypothyroidism, and "prediabetes" without a formal diagnosis of diabetes mellitus.

In the setting of the utility pole accident, he had previously required a percutaneous tracheostomy and gastrostomy for a prolonged intensive care unit stay, both of which had subsequently been removed. He denied other surgery.

He was unsure of the medications that he took on a daily basis. He recalled taking medications for pain control, blood pressure, and for control of his edema, but was unclear of the names or doses of the medications.

He reported no known medication allergies. He lived in New England where he worked in cab dispatch. He had a 120+ pack-year-history of smoking cigarettes but had quit approximately a decade previously. He drank alcoholic beverages on occasion but denied any illicit substances.

Dr Emily Miller: Can you describe his physical examination on presentation to the ED?

Dr Jansson: The vital signs were a temperature of 37.3°C temporally, with heart rate of 108 beats/min and blood pressure of 97/53 mm Hg. He had a respiratory rate of 22 breaths/min and pulse oximetry of 94% on 2 L/min of supplemental oxygen.

He appeared ill but nontoxic. His jugular veins did not appear to be distended and he had no stridor. He was noted to have mild tachypnea, coarse bilateral breath sounds with occasional expiratory wheezing, and a prolonged expiratory phase; he was noted to have pursed-lip breathing. He had a morbidly obese abdomen without any tenderness to palpation. He had symmetric pitting edema to the lower extremities with chronic venous stasis changes. Otherwise, the skin was warm and well-perfused. Neurologically, the patient was awake and fully alert to his surroundings. No cranial nerve deficits were noted and his pupils were equal, round, and reactive to light. He had no focal motor weakness or sensory deficits and was able to perform tests of coordination without dysdiadochokinesis.

Dr Eric Nadel: What was your initial differential diagnosis for this patient?

Dr Jansson: The patient's primary concern on arrival was his dyspnea. An acute exacerbation of COPD was highest on the differential diagnosis, especially given his pursed-lip breathing, wheezing, and new cough. His uncontrollable shaking could also be rigors, raising the possibility of infectious etiology such as pneumonia or a viral process such as influenza. With a positive shock index (heart rate greater than systolic blood pressure), and tachypnea, a diagnosis of sepsis should be considered. The patient's Quick Sequential Organ Function Assessment (qSOFA) indicated that he was at high risk of mortality from sepsis. Although the patient did not recall a diagnosis of heart failure, he had lower extremity edema and was prescribed a diuretic, and so we considered cardiac etiologies, such as heart failure or cardiogenic shock, although these were considered less likely without jugular venous distension and with warm skin.

The patient was initially noted to have altered mental status by the police. On arrival, however, he seemed to be alert and oriented after administration of supplemental oxygen and i.v. glucose, suggesting that the improvement in his mental status was related to either hypoxemia or hypoglycemia. Other transient neurological etiologies, such as a partial seizure or transient ischemic attack, could be considered, but would be less likely.

The etiology of his hypoglycemia was unclear, particularly because the patient reported only having a diagnosis of "prediabetes" and did not recall the names of the medications that he took. However, because his outpatient medication list recorded glipizide as a daily medication, adverse effect of the medication was thought to be most likely.

Dr Andrew Eyre: Would you please describe the initial workup and management of the patient?

Dr Jansson: The patient was placed on continuous cardiac and pulse oximetry monitoring. A repeat POC glucose was obtained, as was a 12-lead electrocardiogram (ECG). A radiograph of the chest was ordered. Blood was sent to the laboratory for a venous blood gas, complete blood count with differential, comprehensive metabolic panel, troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP), and lactic acid. Blood cultures were drawn and cultures of urine and sputum were ordered.

The initial POC glucose measured the whole blood glucose at 37 mg/dL and an additional 25 g i.v. glucose was administered, along with a bolus of normal saline for his hypotension. Given that the diagnosis of sepsis was being considered, with relative hypotension, tachycardia, and tachypnea, broad-spectrum antibiotics were administered. A lung source was thought to be most likely because of his cough and hypoxemia, and so the patient was given ceftriaxone and azithromycin empirically. With his history of COPD, nebulized ipratropium bromide and albuterol sulfate were provided.

Dr David F. M. Brown: What were the results of the initial workup?

Dr Jansson: After the POC glucose, the first information available to us was his 12-lead ECG (Figure 1), showing a sinus tachycardia. There was a right bundle-branch block, new from previous, as well as premature atrial and ventricular beats. The QRS was 156 ms and the QTc was 504 ms. There were no T-wave or ST-segment changes to suggest acute ischemia.

His venous blood gas had a pH of 7.31 and a pCO_2 of 41 mm Hg, suggesting a mixed respiratory and metabolic acidosis. The chemistry panel was notable for metabolic disarray with sodium of 129 mmol/L (reference range 135–145 mmol/L), hemolyzed potassium of 5.9 mEq/dL (reference range 3.4–5.0 mEq/dL), chloride of 90 mmol/L (reference range 98–108 mmol/L), bicarbonate of 18 mmol/L (reference range 23–32 mmol/L), blood urea nitrogen of 78 mg/dL (reference range 8–25 mg/dL), creatinine of 5.16 mg/dL (reference range 0.6–1.5 mg/dL), and measured glucose of 39 mg/dL (reference range 70–110 mg/dL). There was a mild transaminitis with aspartate aminotransferase of 102 U/L (reference range of 10–40 U/L). NT-proBNP was 2161 pg/mL (reference range 0–900 pg/mL) and high-sensitivity troponin was 32 ng/L (reference range 0–14 ng/L).

His complete blood count was notable for a leukocytosis of 29.20 K/μL (reference range 4.5–11 K/μL) with a left shift (94.8% neutrophils). There was no anemia or thrombocytopenia. He was unable to immediately provide a urine specimen. A rapid influenza polymerase

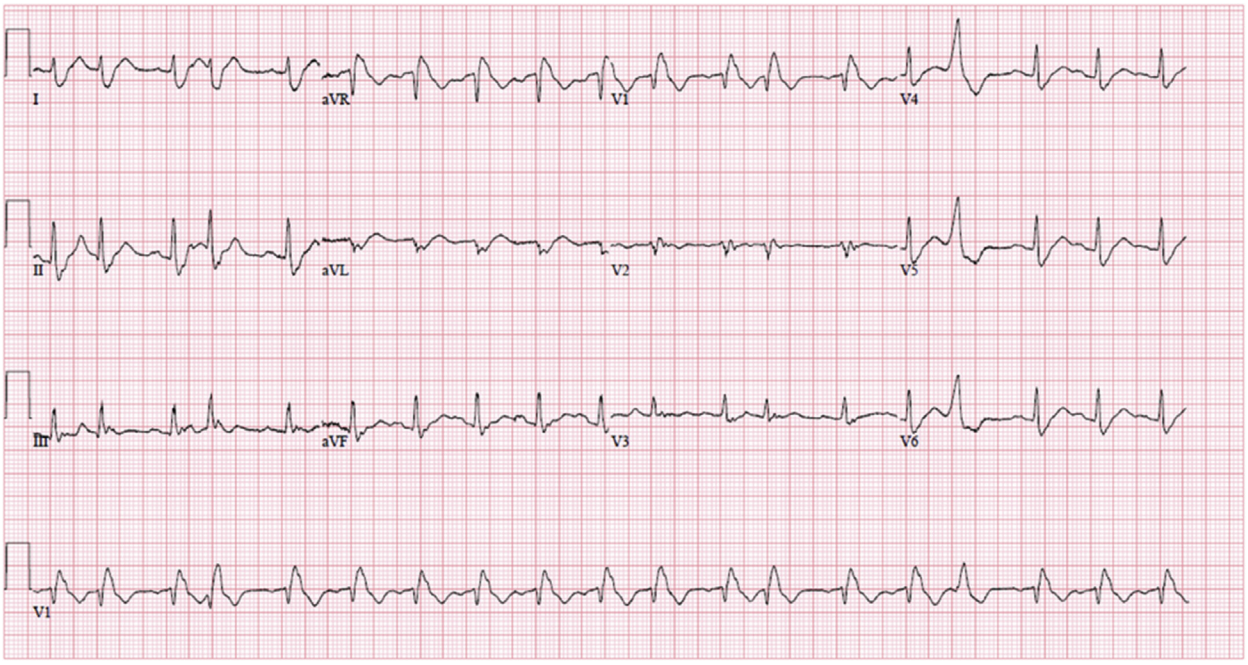

Figure 1. 12-Lead electrocardiogram on arrival.

chain reaction assay was negative for influenza A, B, or the respiratory syncytial virus.

A portable anteroposterior radiograph was obtained (Figure 2). The film was of poor quality, given the patient's morbid obesity, but showed an infiltrate in the right middle and lower lobes and a small right-sided pleural effusion. The radiologist also remarked on enlarged pulmonary arteries.

Dr Ali Raja: How did these initial results affect your differential diagnosis and management?

Dr Jansson: Most striking in his initial laboratory testing was his creatinine of 5.16 mg/dL, suggestive of acute renal failure. The patient's reported decreased urine output over the last 2 days took on particular significance, as post-renal obstructive etiologies can cause acute kidney injury. POC ultrasonography was performed. Although technically difficult due to the patient's body habitus, a collapsed bladder and no signs of ureterohydronephrosis were noted, suggesting either a pre-renal or intrinsic kidney injury. A Foley catheter was placed for close monitoring of urine output and a specimen was sent to the laboratory for urinalysis and culture. The urinalysis did not show pyuria or bacteria. Although the initial serum potassium was elevated, the specimen was grossly hemolyzed and there were no ECG changes consistent with hyperkalemia, therefore, we re-sent the test and deferred empiric treatment for hyperkalemia. Because his pH was not severely acidemic and he did not have evidence of significant pulmonary edema or volume overload, we did not think that emergent dialysis was indicated.

In the setting of a productive cough, hypoxemia, and tachycardia, the radiograph showing a right-sided infiltrate and the profound leukocytosis with a left shift supported a diagnosis of pneumonia, likely bacterial. As the patient reported no recent hospitalizations or exposure to i.v. antibiotics, treatment for community-acquired pneumonia was continued (1). His venous blood gas showed a normal pCO_2, ruling out hypercarbia as a cause of his altered mental status. With the report of uncontrollable shaking chills 2 days prior, bacteremia should be considered. Although the NT-proBNP and troponin were mildly elevated, a primary cardiogenic

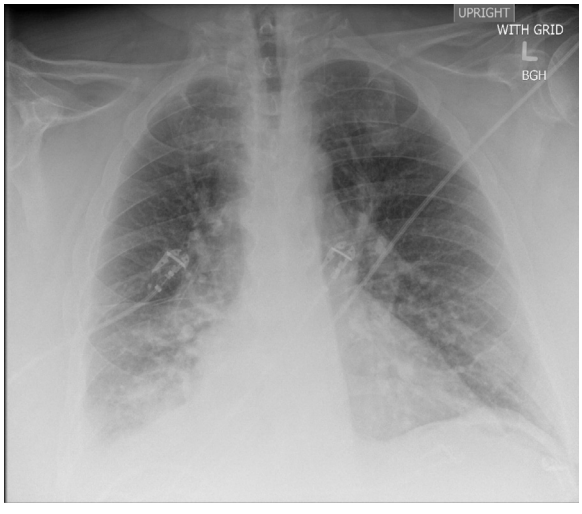

Figure 2. Anteroposterior radiograph of the chest on arrival.

etiology was less likely, particularly without any other signs of right-heart failure.

Dr Susan Wilcox: Would you please review the differential diagnosis of hypoglycemia?

Dr Jansson: The differential diagnosis of hypoglycemia is extremely broad and includes more than 100 causes (2). However, the vast majority of cases occur in diabetic individuals and are caused by insulin or other hypoglycemic medications (3,4). In patients without diabetes or exposure to hypoglycemic medications, there are several causes worth considering. Decreased oral intake is typically compensated by gluconeogenesis and glycogen metabolism, but can cause hypoglycemia in the setting of malnourishment (5). Particularly in the ED, ethanol can be a significant cause of hypoglycemia, particularly in the setting of binge drinking, as a result of glycogen depletion and inhibition of gluconeogenesis (6).

Hypoglycemia is not uncommon in the critically ill patient. Cytokine release in sepsis can lead to hypoglycemia when gluconeogenesis cannot compensate for increased glucose utilization (7). Hormone deficiency, such as that found in Addison's disease (cortisol deficiency); primary or secondary adrenal insufficiency; or adrenocorticotropic hormone deficiency, has been reported to cause hypoglycemia, but typically present with other symptoms of adrenal insufficiency (3).

Tumors that secrete hormones can cause hypoglycemia. The classic but rare case is that of an insulinoma, an islet cell tumor that produces insulin but is not sensitive to downregulation in the setting of hypoglycemia (8). Nonislet cell tumors have also been linked to hypoglycemia, typically due to overproduction of insulin-like growth factor-2 (9).

Finally, accidental or intentional administration of a hypoglycemic medication can cause hypoglycemia. Covert or malignant administration of insulin has been seen in the factitious syndromes, including Munchausen syndrome and Munchausen-by-proxy (10).

Dr Emily Hayden: Review of pharmacy records indicated that the patient was prescribed amitriptyline, sustained-release morphine, and a combination oxycodone-acetaminophen tablet for his chronic pain, and a low dose of furosemide for his peripheral edema. He was prescribed hydrochlorothiazide and lisinopril for hypertension and levothyroxine for hypothyroidism. He took a combination mometasone-formoterol inhaler for his COPD with albuterol as needed, and took glipizide for his elevated blood glucose.

At this point, our working diagnosis was that a pneumonia had led to severe pre-renal injury of his kidneys, causing a relative overdose of glipizide, which was responsible for his recurrent hypoglycemia.

Dr Edward Boyer: Would you please review the management of hypoglycemia induced by overdose of the commonly used diabetic medications?

Dr Jansson: As with most poisonings, high-quality supportive care is the foundation of management. Expert consultation and involvement of the local poison control center are advised.

Insulin is responsible for the majority of medication-induced hypoglycemia (11). The mainstay of treatment is supplemental dextrose, orally if tolerated, or intravenously if needed. An initial bolus of 0.5–1 g/kg is provided intravenously, followed by a titrated dextrose infusion until euglycemia or slight hyperglycemia is achieved. The duration of observation and treatment is guided by the medication, dose, and route of administration. Longer-acting formulations and higher doses of insulin will require longer observation periods (12). Large injection volumes require longer observation because of both the dose of the medication and the possible depot effect (11).

Sulfonylureas comprise the other most commonly implicated class of drugs responsible for hypoglycemia. The sulfonylureas (glipizide, glyburide, and glimepiride) act by stimulating insulin release from the pancreatic β-islet cells (13). These medications have a narrow therapeutic index and hypoglycemia has been reported in children with as little as one pill ingested (11). As with insulin, the mainstay of treatment is supplemental dextrose, orally or intravenously. In contrast to insulin, supplemental glucose has a synergistic effect with the sulfonylureas on the pancreatic islet cells to increase insulin release, leading to a paradoxical or relative hypoglycemia in some patients (14). For patients requiring repeated bolus dosing of dextrose or refractory hypoglycemia, octreotide should be administered (15). Octreotide is a synthetic somatostatin analogue that antagonizes the calcium channel opened by the sulfonylureas (16). Patients should be observed until euglycemic.

The meglitinides include neteglinide and repaglinide; their mechanism of action is similar to the sulfonylureas, but they have a much shorter duration of action. Overdose is rare. Management is similar, with supplemental glucose, octreotide, or activated charcoal as needed (14).

Metformin is the only commercially available biguanide available in the United States (17). Its mechanism of action is complex and includes decrease in hepatic glucose production and increased peripheral insulin sensitivity (18). Hypoglycemia is uncommon in overdose, but the feared complication is metformin-associated lactic acidosis (MALA). Profound metabolic (lactic) acidosis occurs and can be accompanied by hypotension and shock. MALA is seen most commonly in overdose and in patients with reduced renal function. Intensive supportive care is indicated, including i.v.

fluids, sodium bicarbonate infusion, vasopressors, and hemodialysis, if clinically indicated. Activated charcoal may be considered for gut decontamination.

Thiazolidinediones (rositglitazone and pioglitazone) belong to the class of peroxisomal proliferator-activated receptor–γ agonists and function as insulin sensitizers. Although chronic therapy has been linked with hepatic injury, overdose is typically well-tolerated (14). α-Glucosidase inhibitors (acarbose and miglitol) prevent the metabolism and absorption of carbohydrates in the small intestine. Overdose has not been reported.

Glucagon-like peptide-1 (GLP-1) is expressed in the intestines to regulate insulin secretion and is degraded by the enzyme dipeptidyl peptidase 4 (DPP-4) (17). Medications used for diabetes include GLP-1 mimics (exenatide and liraglutide) and DPP-4 inhibitors (sitagliptin, saxagliptin, and linagliptin). Although only a few case reports have been published, they appear to be well-tolerated in overdose, with one case report of liraglitide causing hypoglycemia (19–22).

Amylin is secreted from β cells in the pancreas with insulin and acts to delay gastric emptying, promote satiety, and inhibit glucagon secretion. Pramlintide is the only amylin analogue marketed in the United States. Overdose has not been reported but hypoglycemia could be expected (17).

Dr Christopher Kabrhel: What was this patient's ED course?

Dr Jansson: Shortly into his ED visit, the patient became hypotensive. A second bolus of i.v. crystalloid was administered, with minimal effect. With his previously documented history of peripheral edema, the elevated NT-proBNP and pulmonary artery enlargement on chest radiograph, we decided to initiate vasopressors instead of further fluid resuscitation, given the concern for possible heart failure. The patient was started on i.v. norepinephrine with improvement in his mean arterial pressure. With his hypotension requiring vasopressors, high qSOFA score, and concern for infection, his antibiotics were broadened to include vancomycin.

After the bolus crystalloid and antibiotics, a repeat basic metabolic panel and venous blood gas were drawn. The blood gas showed worsening of his acidemia, with pH of 7.25 and pCO_2 of 44. His sodium had improved, however, to 133 mmol/L and his creatinine improved to 4.67 mg/dL. Nephrology consultation was sought, who thought that the etiology of his renal failure was prerenal from hypovolemia. Because his creatinine was improving with the administration of i.v fluids, they agreed with the decision to defer dialysis for now, but recommended administration of sodium bicarbonate given the acidemia.

He had two more episodes of recurrent hyperglycemia in the ED. After the second recurrent episode, he was started on a continuous infusion of dextrose-containing i.v. fluid and a continuous infusion of octreotide. He was admitted to the intensive care unit.

Dr J. Kimo Takayesu: What was the patient's ultimate course?

Dr Jansson: The patient recovered well in the intensive care unit. His blood cultures grew *Streptococcus pneumoniae* in 3 out of 4 bottles and he ultimately completed a course of levofloxacin. Echocardiography revealed a structurally normal heart with normal function. He briefly required supplemental oxygen via a nasal cannula but never required intubation or noninvasive ventilation. His creatinine and renal function normalized within 3 days and the patient never required renal replacement therapy. The patient ultimately was discharged home and was lost to follow-up.

Dr Wilcox: What are the key learning points from this case?

Dr Jansson: Although there are numerous causes of hypoglycemia, the vast majority occur in patients with diabetes and are attributed to adverse effects or overdose of insulin or other diabetic medications. Supportive care with close glucose monitoring and supplemental glucose administration is the mainstay of treatment for overdose, with two classes requiring special consideration. The sulfonylureas are commonly implicated in hypoglycemia because of their narrow therapeutic index and may require administration of octreotide, while metformin has been linked to a severe lactic acidosis, particularly in patients with renal dysfunction. The remainder of the oral diabetic medications are generally well tolerated in overdose.

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