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How could hypoglycemia-inducing glycogen storage disease lead to hyperglycemia-induced mucormycosis?

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ABSTRACT

Mucormycosis is an increasingly frequent, difficult to diagnose, difficult to treat, often fatal infection, especially in patients with hyperglycemia from uncontrolled diabetes. Type I (von Gierke) glycogen storage disease is due to inherited deficiency of enzymes in glycogen metabolism, which causes hypoglycemia. This report is the case of a patient with von Gierke disease and a missed diagnosis of pulmonary mucormycosis. This report illustrates the importance of having a high index of suspicion for mucormycosis in the appropriate clinical context.

Keywords
Mucor; Lung Diseases, Fungal; Glycogen Storage Disease Type I; Autopsy

CASE REPORT

This 20-year-old woman from the Northeast USA had type I (von Gierke) glycogen storage disease and was transferred to a referral hospital for liver transplant evaluation. The patient had received a living-related renal transplant at age 15 for renal failure attributed to her glycogen storage disease. She had had a laparoscopic cholecystectomy at age 18. She had developed chronic rejection of her renal transplant and hemodialysis had to be resumed approximately 10 months prior, at which point immunosuppression was presumably stopped. One week prior to transfer, she received a second living-related renal transplant. Three days postoperatively, the transplant renal vein thrombosed. Five days postoperatively, the new allograft was removed. Following the allograft nephrectomy, the patient had increasing transaminases, prothrombin time, partial thromboplastin time and lactate. Her platelet count and hemoglobin fell. She became obtunded and hypotensive. The patient was intubated and mechanically ventilated. An infusion of dopamine was started for blood pressure support. She was given platelets, packed red blood cells, fresh frozen plasma, cryoprecipitate and desmopressin. She was transferred to a referral hospital on postoperative day 7 for liver transplant evaluation.

On admission to the referral hospital, the patient's temperature was 36 degrees C, pulse 100/minute, respirations 16/minute (on ventilator) and blood pressure 110/60 mm Hg. Her abdomen was diffusely tender with serous drainage from her surgical drain. She was incontinent of stool and had pedal edema. Neurologic examination showed a grade III hepatic coma, with grimacing to pain. She was mildly hyperreflexic. Blood testing showed multi-organ biochemical derangement with ammonia 108 uMol/L (reference range [RR]: 5-50 uMol/L), lactate 21.7 mEq/L (RR: 0.7-1.8 mEq/L), and bilirubin 12.7 mg/dL

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(RR: 0.3-1.5 mg/dL). Tissue injury was manifested by elevated serum aspartate aminotransferase (AST) 18,895 U/L (RR: <40 U/L), alanine aminotransferase (ALT) 2659 U/L (RR: <40 U/L), and amylase 1570 U/L (RR: 25-125 U/L). Additional metabolic testing revealed serum sodium 136 mEq/L (RR: 136-145 mEq/L), potassium 6.2 mEq/L (RR: 3.5-5.1 mEq/L), chloride 89 mEq/L (RR: 95-110 mEq/L), bicarbonate 11 mEq/L (RR: 21-31 mEq/L), calcium 7.3 mg/dL (RR: 8.5-10.5 mg/dL), phosphorus 14.3 mg/dL (RR: 2.5-4.5 mg/dL), magnesium 1.7 mEq/L (RR: 1.6-2.5 mEq/L), glucose 331 mg/dL (RR: 70-110 mg/dL), blood urea nitrogen 8 mg/dL (RR: 9-20 mg/dL), and creatinine 3.7 mg/dL (RR: 0.8-1.5 mg/dL). The patient's hemoglobin was 7.4 g/dL (RR: 11.7-15.7 g/dL), and white blood cell count 10,100/mm^3 (RR: 4,000-10,000/mm^3). She was coagulopathic with platelets 52,000/mm^3 (RR: 140,000-440,000/mm^3), prothrombin time (PT) 21.8 seconds (RR: 10.5-13 seconds), and partial thromboplastin time (PTT) 57.8 seconds (RR: 25-33 seconds). Arterial blood showed pH 7.12, PCO2 32 mm Hg and PO2 134 mm Hg. Chest x-ray showed no pulmonary edema.

The patient was admitted with diagnoses of fulminant hepatic failure, coagulopathy, metabolic acidosis, renal failure and anemia. Computed tomography (CT) scan of the head showed no intracranial bleeding. Transcranial Doppler examination showed slightly increased cerebral blood flow. CT scan of the abdomen showed an enlarged liver, and an ultrasound examination of the abdomen had findings that suggested the possibility of hepatic vein thrombosis, but was not definitive. The patient was given red blood cells, platelets, fresh frozen plasma, cryoprecipitate, bicarbonate, and started on slow continuous ultrafiltration dialysis. Cefotetan and vancomycin therapy were started.

The following day, the patient was weaned from dopamine. Her transaminase values decreased and her lactate decreased to 19.1 mEq/L. Abdominal CT scan showed a lower chest infiltrate consistent with infection or posttransplant lymphoproliferative disorder. Her amylase rose to 3113 U/L. Blood cultures drawn on admission were reported positive for gram positive cocci in pairs and chains. Later that day, the patient developed an unstable heart rhythm. She was started on esmolol.

On the third day at the referral hospital, the patient remained unresponsive. Her lactate and transaminases continued to fall, but lipase increased above 4000 U/L and bilirubin climbed to 22 mg/dL. The admission blood culture isolate was identified as Enterococcus faecalis. Arterial line catheter tip culture from admission yielded Enterococcus faecium and Enterococcus faecalis.

On the fourth day, the patient continued in hepatic coma and shock, with metabolic acidosis (lactate 27.9 mEq/L). She had diffuse 2+ edema and bilateral rhonchi. Blood and sputum cultures from the third day were positive for Enterococcus faecalis. At 13:30, the patient's Swan Ganz right heart catheter was changed and culture of the catheter tip subsequently yielded 100 colonies of Enterococcus faecalis. At 18:28, the patient's bilirubin was 25.8 mg/dL, ALT 619 U/L, AST 5224 U/L, PT 20.4 seconds, PTT 34.8 seconds, sodium 129 mEq/L, potassium 3.3 mEq/L, chloride 81 mEq/L, bicarbonate 19 mEq/L, blood urea nitrogen 3 mg/dL, creatinine 1.7 mg/dL, glucose 504 mg/dL, white blood cell count 8,100/mm^3 (83% segmented neutrophils, 8% bands, 2% lymphocytes, 7% monocytes), hemoglobin 10.5 g/dL, and platelets 24,000/mm^3.

Considering that the patient's liver might be the anatomic source of her life-threatening enterococcal sepsis and was non-functional, a decision was reached to perform an emergency hepatectomy with a portocaval shunt and hope of soon finding a suitable liver for transplantation. During the procedure, the patient needed 91 units of blood, 30 units of platelets, and 24 units of cryoprecipitate and fresh frozen plasma. As the surgeons were closing the abdomen, the patient became bradycardic and started bleeding through her endotracheal tube. Arterial blood showed pH 7.15, PCO2 27 mm Hg and PO2 59 mm Hg. Cardiopulmonary resuscitation including pericardiocentesis with removal of 200 ml of fluid was to no avail.

The explanted liver weighed 3700 grams (RR: <1800 grams) and showed near-total necrosis with massive hemorrhage, but no significant inflammation and no organisms on special stains. Neither the surgical pathology examination of the explanted liver nor the autopsy showed hepatic vein thrombosis.

AUTOPSY FINDINGS

Postmortem examination revealed massive internal hemorrhage in the lungs, pleural spaces, gastrointestinal tract, genitourinary tract and left adrenal gland. Autopsy also demonstrated mucormycosis in left upper lobe lung with vascular invasion and areas of associated hemorrhagic pulmonary infarction (Figure 1).

In areas without infarction or hemorrhage, the lungs had moderate alveolar edema (Figure 2).

Postmortem lung cultures yielded Rhizopus. The remaining allograft kidney (the first one transplanted) showed moderate chronic rejection.

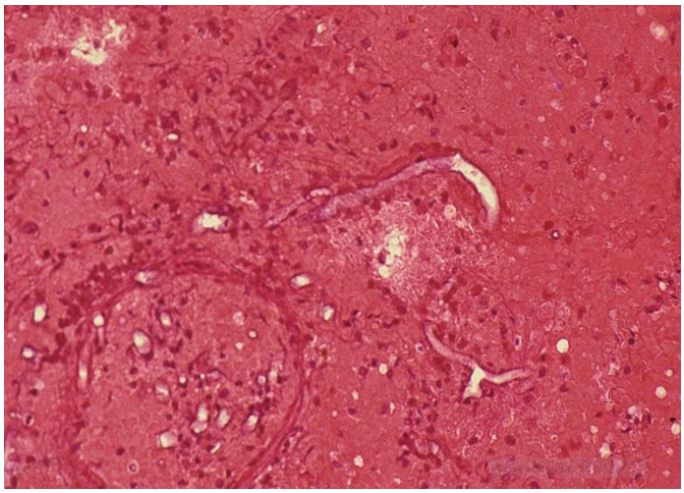

Figure 1. Photomicrograph of the lung showing an area of hemorrhagic infarction shows large pauciseptate fungal hyphae, with low protein content giving some hyphae an empty appearance and one of these with right-angle branching (H&E, 250X).

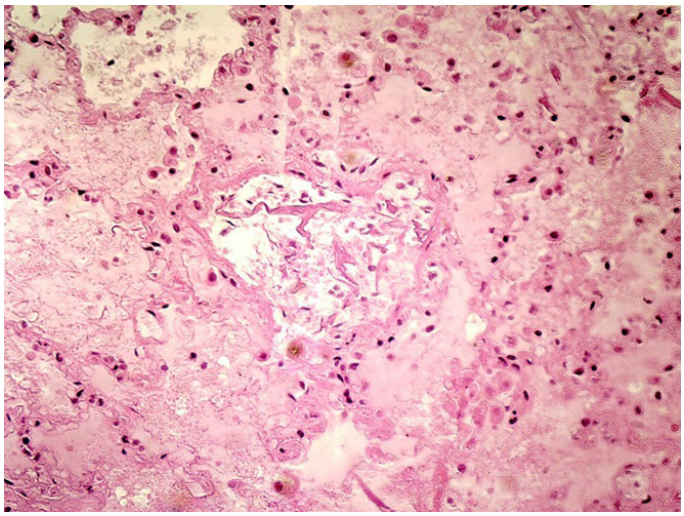

Figure 2. Photomicrograph of the lung showing area of alveolar edema shows fungal hyphae with random-angle branching and collapse in the crumpled ribbon configuration characteristic of mucormycosis (H&E, 250X).

The native kidneys showed diffuse sclerosis of glomeruli with interstitial edema, fibrosis and tubular atrophy. The autopsy also showed a 4.8 cm superior vena cava peri-catheter thrombus, fibrin thrombi in glomeruli and blood vessels consistent with disseminated intravascular coagulation, and multifocal pancreatitis.

DISCUSSION

The antemortem and postmortem evidence suggests that the immediate primary cause of this patient's death was massive internal bleeding, associated with pulmonary mucormycosis, gut ischemia, coagulopathy and the anhepatic state. The enterococcal sepsis preceding this was presumably from the intestines, possibly due to ischemia, but the brief immunosuppression for the failed second renal transplantation may have contributed. Bleeding from left upper lobe lung, with blood pouring into the endotracheal tube, seems to have precipitating the patient's terminal cardiopulmonary arrest. This pulmonary bleeding was related to angioinvasive pulmonary mucormycosis.

Lung is often the first site of mucormycosis, as exemplified in this case. The nose is even more often the first site of mucormycosis.[1] The respiratory tract, upper or lower, is usually the first site of infection because infection usually starts with inhalation of spores. These spores are ubiquitous in the air all around the world.[2] Infection is not with the inhaled resting spore forms, but with hyphal forms of the mucoralean fungi. One virulence factor of the mucoralean fungi is rapid germination from spores to hyphae.[3] Rapid growth of the hyphae is another virulence factor. Rhizopus species inhibit phagosome maturation in macrophages by the melanin on the spore surface.[2] Rhizopus species also resist being damaged or killed by decreasing the oxidative burst of phagocytes, which is another virulence factor.[3] Spore coat protein CotH of mucoralean fungi binds to glucose-regulated protein 78 (GRP78) on endothelial cells, promoting angioinvasion, which results in thrombosis and tissue necrosis, yet another virulence factor.[2] The endothelial expression of GRP78 is increased in diabetic ketoacidosis, which brings us to the host factors in mucormycosis.

Mucormycosis is rare in patients without uncontrolled diabetes, neutropenia, immunosuppression or hematologic malignancy.[1] These conditions are all becoming more common and the incidence of mucormycosis is similarly increasing.[4] Pulmonary mucormycosis makes up a quarter of the cases and has a fatality of approximately 50%. The most prevalent underlying disease in patients with pulmonary mucormycosis, in 51 to 79% of cases, is hematologic malignancy.[1] Among patients with hematologic malignancy and pulmonary mucormycosis, specific risk factors for this infection are neutropenia (80% of cases), corticosteroid therapy (26%), stem cell transplantation (24%), diabetes (18%), and graft-versus-host disease (10%).[1] The patient of this case report underwent brief immunosuppression for 5 days for her second renal transplantation, ending 5 days before her demise, but her last lymphocyte count was 162/mm^3 (RR: 1,000-4,200/mm^3), suggesting that she had residual immunosuppression predisposing her to infection.

Pulmonary mucormycosis can be difficult to recognize because symptoms of the infection are nonspecific. Clinical manifestations, which correlate with angioinvasion, include fever, cough, chest pain, dyspnea and hemoptysis.[1] On radiologic imaging, pulmonary mucormycosis presents most often as nodules, areas of consolidation, cavitary lesions or pleural effusion.[5] On CT scan, nodules of mucormycosis may have surrounding ground-glass opacity (halo sign) or a central ground-glass opacity may have surrounding consolidation (reverse halo sign). Reverse halo sign is particularly suggestive of mucormycosis.[5,6] In the patient of this case report, the lungs had hemorrhages and edema in addition to mucormycosis, which likely obscured findings typical of mucormycosis.

The diagnosis of mucormycosis is challenging.[7] The agents of mucormycosis do not have 1,3-beta-D-glucan or galactomannan in their cell walls, so serum tests for beta-D-glucan and galactomannan are not helpful in making the diagnosis of mucormycosis. It relies on the identification of organisms in tissue by histopathology with culture confirmation, but culture often yields no growth, leaving the pathologist's identification of this type of mycosis as the only basis for the diagnosis. Fortunately, Rhizopus and the other agents of mucormycosis do have morphology distinct from other fungal pathogens: large hyphae with scant random-angle branching, empty-appearing due to low protein content, and collapse in a crumpled ribbon configuration.[8,9] This morphology is illustrated in the case of this report. The pathologist's diagnosis in this case was confirmed by culture, but the agents of mucormycosis can colonize the airways or be contaminants in cultures, so the isolation of these fungi in a culture does not prove infection. Culture results must be interpreted in the context of the patient's symptoms, signs, and underlying disease to determine whether antifungal therapy should be started.

Mucormycosis typically has a rapid clinical progression.[7] A clinician must think of this infection in the appropriate clinical setting and quickly pursue invasive testing in order to establish a diagnosis as early as possible. Diabetic ketoacidosis and neutropenia are two of the most common clinical settings for mucormycosis. Diplopia in a patient with diabetic ketoacidosis or hemoptysis in a patient with neutropenia should immediately suggest the diagnosis of mucormycosis. Black tissue necrosis in the nose, periorbital region or other sites of infection is the gross pathologic hallmark of mucormycosis.[7,9] To be successful, therapy must be prompt.

The treatment of mucormycosis is challenging.[7] Rhizopus and the other agents of mucormycosis are not susceptible to most antifungal drugs, including voriconazole. Successful treatment often requires a combination of intravenous amphotericin B (lipid formulation) and surgical debridement of necrotic infected tissue. Wide debridement to include surrounding healthy-appearing tissue is necessary because the hyphae invade so rapidly that the leading edge of infected tissue is not visibly necrotic. Global guidelines for the diagnosis and management of mucormycosis have recently been promulgated.[9] Successful treatment frequently depends on reversing the underlying condition such as neutropenia or diabetic ketoacidosis that allowed infection by mucoralean fungi.

This patient's underlying condition was glycogen storage disease type I, also known as von Gierke disease, which is an inherited disorder caused by deficiencies of enzymes in glycogen metabolism.[10]

It was first described by von Gierke in 1929 who reported excessive hepatic and renal glycogen in the autopsies of two children. In the most common form of type I glycogen storage disease, there is a deficiency of glucose-6-phosphatase, which cleaves glycogen to glucose, leading to hypoglycemia and lactic acidosis, Patients present with manifestations of hypoglycemia and metabolic acidosis, typically around 3 to 4 months of age. Diet and lifestyle changes are made to prevent the primary concern of the disease, hypoglycemia. Initially, infants are fed soy-based, sugar-free formula on demand every 2 to 3 hours. Cornstarch has been used for the treatment of hypoglycemia since its slow digestion provides a steady release of glucose. When an infant's sleep duration becomes longer than 3 to 4 hours, it is important to prevent hypoglycemia during sleep, which can be done by administering tube feed via a nasogastric tube or a surgically placed gastric tube.[10] Prevention of hypoglycemia is paramount in the treatment of von Gierke disease.

How could this patient's hypoglycemia-inducing glycogen storage disease have led to mucormycosis, which is typically hyperglycemia-induced? The patient's blood glucose was 331 mg/dL on admission to the referral hospital and 504 mg/dL 8 hours before she died in the operating room. The physicians at both hospitals seem to have been so worried about the possibility of hypoglycemia that they gave so much glucose that the patient had hyperglycemia equivalent to diabetes out of control.

CONCLUSION

This is the report of a case of a missed diagnosis of pulmonary mucormycosis in a patient with glycogen storage disease. The patient was critically ill, with multi-organ system failure and enterococcal sepsis, following a failed kidney transplantation. With the stress response to her critical illness, the glucose infusion to prevent hypoglycemia from the patient's underlying disease resulted in hyperglycemia in the range of diabetic ketoacidosis, a major risk factor for mucormycosis. One lesson from this case might be expressed: Watch out for mucormycosis. Another lesson might be expressed: Be careful not to overcorrect for hypoglycemia. Primum non nocere.

Informed consent by the next of kin was retained by the institution where the autopsy was performed, whose institutional review board waives approval of case report manuscripts.

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