You're The Flight Surgeon

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You are the flight surgeon stationed at a pilot instructor base. You are notified that one of your instructor pilots was taken to the emergency department via ambulance with symptoms of tremulousness, diaphoresis, and confusion. Upon further questioning, the pilot reported similar episodes throughout the past several years. He reports lightheadedness and tremulousness during fasting of 3 h or more, which has led him to eating frequent meals and carrying snacks with him at all times to prevent the episodes. Although these symptoms had occurred for the last several years, he attributed this phenomenon to a fast metabolism and did not seek medical care for this specific issue.

He has no pertinent past medical history or surgical history. He denied any recent illnesses or injuries. He takes no medications. He is married with several children, all of whom are healthy. He has no known family medical history.

1. What would be your next best step in evaluation of his symptoms?

A. Blood glucose evaluation.
B. Computed tomography (CT) of the head.
C. Cardiac enzymes/electrocardiogram.
D. Blood cultures/complete blood count.

ANSWER/DISCUSSION

1. A. The patient exhibits classic symptoms of hypoglycemia, which are divided into two groups: autonomic and neuroglycopenic. Autonomic symptoms include palpitations, tremor, anxiety, sweating, hunger, and parasthesias. Neuroglycopenic symptoms include dizziness, weakness, drowsiness, and confusion.[9] Due to the patient's symptoms, blood glucose evaluation is warranted as the next best step. A fingerstick blood glucose is likely the most readily available and most efficient way of checking glucose. A low fingerstick blood glucose should then be validated with plasma glucose evaluation, as plasma (or serum) blood glucose evaluation is the most accurate glucose assessment when glucose values are $< 75\ mg \cdot dL^{-1}$.

On-scene paramedics measured a fingerstick glucose of $37\ mg \cdot dL^{-1}$ during a fasting period. The patient was given dextrose with normalization of plasma blood glucose and resolution of his symptoms. He was admitted to the internal medicine inpatient service at a nearby hospital for further evaluation.

2. What would be your next step in the evaluation of hypoglycemia?

A. Glucagon challenge.
B. Mixed meal test.
C. 72-h fast.
D. CT of the abdomen.

ANSWER/DISCUSSION

2. C. Suspected fasting hypoglycemia in a patient without diabetes which cannot be recreated via an outpatient fasting scenario is best evaluated with a supervised 72-h fast. This can help differentiate between various etiologies of hypoglycemia. Causes of hypoglycemia in adults who do not have diabetes mellitus include insulin-producing tumors, nonislet cell tumors, critical illness, postgastric bypass hypoglycemia, insulin autoimmunity, or cortisol deficiency.[3] Alcohol and drugs, including insulin, insulin secretagogues, gatifloxacin, pentamidine, indomethacin, and glucagon can also cause hypoglycemia.[3]

During a 72-h fast, a patient consumes no food and only beverages that are calorie and caffeine free. Fingerstick blood glucose testing is performed at regular intervals and more frequently if the patient experiences symptoms of hypoglycemia. The fast is ended when any of the following conditions are met: the patient has a plasma blood glucose level of $\leq 45\ mg \cdot dL^{-1}$, symptoms of hypoglycemia, 72 h have elapsed, or when the plasma glucose is less than 55 with demonstration of Whipple's triad. Whipple's triad consists of plasma-verified hypoglycemia, hypoglycemic symptoms, and resolution of symptoms after the plasma glucose is corrected.[1] When the patient has symptoms of hypoglycemia and point of care blood glucose is ≤ 55, blood specimens of plasma glucose, insulin, C-peptide, proinsulin, and beta-hydroxybutyrate are collected and sent to the lab for processing. A sulfonylurea and meglitinide screen should also be

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collected. Then 1 mg of glucagon is given intravenously and plasma glucose is measured 10, 20, and 30 min after administration. This assesses the glycemic response to glucagon and can help determine if the hypoglycemia is insulin mediated. The patient may then eat. The results of the laboratory assessment help differentiate between different causes of hypoglycemia.

The patient's 72-h fasting protocol was terminated at the 18-h mark when the patient's point of care blood glucose was measured at 24 mg · dL^{-1} with neuroglycopenic symptoms present. Labs drawn simultaneously were significant for a plasma blood glucose of 27 mg · dL^{-1} [normal (nl) 74–109 mg · dL^{-1}], insulin of 56.4 mcIU · mL^{-1} (nl 2.6–24.9 mcIU · mL^{-1}), proinsulin of 145.8 pmol · L^{-1} (nl 0.0–10.1 pmol · L^{-1}), and a C-peptide of 8.91 ng · mL^{-1} (nl 1.1–4.4 ng · mL^{-1}). Upon termination of the test, glucagon was administered with subsequent rise in plasma glucose and resolution of neuroglycopenic symptoms. Sulfonylurea, urine drug screen, and insulin antibody testing was negative. A three-phase pancreatic CT was performed and did not demonstrate any focal pancreatic mass or irregularities. The patient was able to maintain euglycemia with frequent oral intake alone and was discharged to home.

3. The patient returns to your flight medicine clinic. What is your recommendation?

A. Return to flying status as he is maintaining a normal glucose.
B. Recommend permanent disqualification.
C. Duty not involving flying and refer to general surgery for evaluation.
D. Place on duty not involving flying and refer to endocrinology for evaluation.

ANSWER/DISCUSSION

3. D. The next appropriate step is to refer the patient to endocrinology for further assessment. The patient exhibited evidence of fasting hypoglycemia. The patient had a low plasma blood glucose and elevated insulin, C-peptide, and proinsulin levels. Insulin antibody testing and testing for oral hypoglycemic medications were negative. He had an appropriate rise in plasma blood glucose with glucagon administration. These lab findings are suggestive of insulinoma or noninsulinoma pancreatogenous hypoglycemia syndrome.

The patient was referred to endocrinology, which determined further imaging was indicated to assess for insulinoma despite no evidence of a lesion on CT of the abdomen. Multiple imaging modalities may be needed to localize an insulinoma, including CT, magnetic resonance imaging, endoscopic ultrasound, and ^{68}Ga-Dotatate positron emission tomography (PET)/CT. The choice of imaging depends on local health system availability, expertise, and need for further evaluation based on initial imaging results. Insulinomas are the most common type of functional pancreatic endocrine tumor, but occur rarely with four cases per 1 million people per year.[5] The median duration of symptoms before diagnosis is 18 mo, but some patients are symptomatic for decades prior to diagnosis.[8] Insulinomas are almost always benign, single lesions located in the pancreas.[6] A ^{68}Ga-Dotatate PET/CT (**Fig. 1**) demonstrated a 19 × 16-mm lesion of the distal pancreatic tail, which was favored to represent a primary insulinoma.

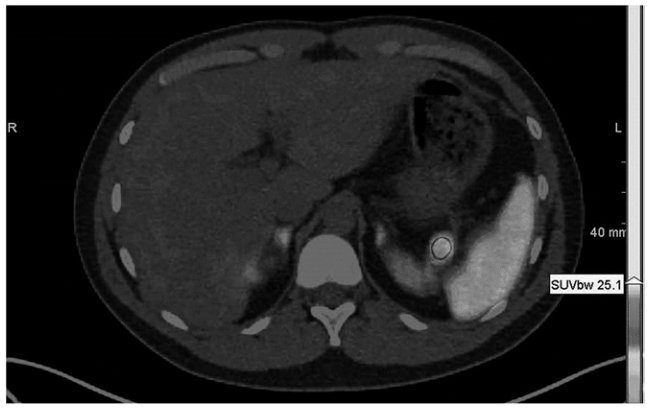

Fig. 1. ^{68}Ga-Dotatate PET/CT.

4. What is the next recommended step?

A. Chemotherapy.
B. Surveillance.
C. Dietary modification with acarbose.
D. Surgical resection.

ANSWER/DISCUSSION

4. D. The patient underwent robotic-assisted laparoscopic distal pancreatectomy (**Fig. 2**) without complications. Pathology confirmed a 13 × 12 × 8-mm insulinoma based on staining patterns. The imaging modality used for postsurgical surveillance in patients with an insulinoma is personalized and is typically based on initial diagnostic imaging modalities. Our patient's surgeon recommended repeat ^{68}Ga-Dotatate PET/CT at 1 yr postsurgery.

The treatment of choice for insulinoma is surgical resection.[1] Because the vast majority of insulinomas are isolated, benign lesions, complete surgical resection is considered curative. Diazoxide is a medication that acts on beta cells to decrease insulin secretion and can be considered for preoperative treatment to help minimize hypoglycemia prior to surgery.[1] In patients who are asymptomatic 6 mo after surgery, only 6% will develop recurrence of hypoglycemia in the 10 yr after surgery.[8]

Insulinoma is addressed by section M30, hypoglycemia from any endogenous source, of the U.S. Air Force Medical Standards Directory (MSD).* The standard does not apply for retention or for operational support flight duties, but a waiver is required for Flying Class I/IA, II, III, remotely piloted aircraft pilots, missile operations duty, and ground-based controller duties. Section O2 of the

*U.S. Air Force. Section M: endocrinology and metabolic USAF medical standards, M30. Section O: tumors and malignancies USAF medical standards, O2. In: Medical standards directory (MSD). 2019:50, 54. [Accessed 1 Apr. 2019]. Available from https://kx2.afms.mil/kj/kx4/FlightMedicine/Documents/Forms/ShowFolders.aspx?RootFolder=%2Fkj%2Fkx4%2FFlightMedicine%2FDocuments%2FMedical%20Standards%20Directory%20%28MSD%29%2F2019&FolderCTID=0x0120004DEB19A0C597EF4794DF99094B5AD8FC&View=%7BE6B00DAE%2DE012%2D41B4%2DB351%2DDDE160D7DA68D%7D to those with access.

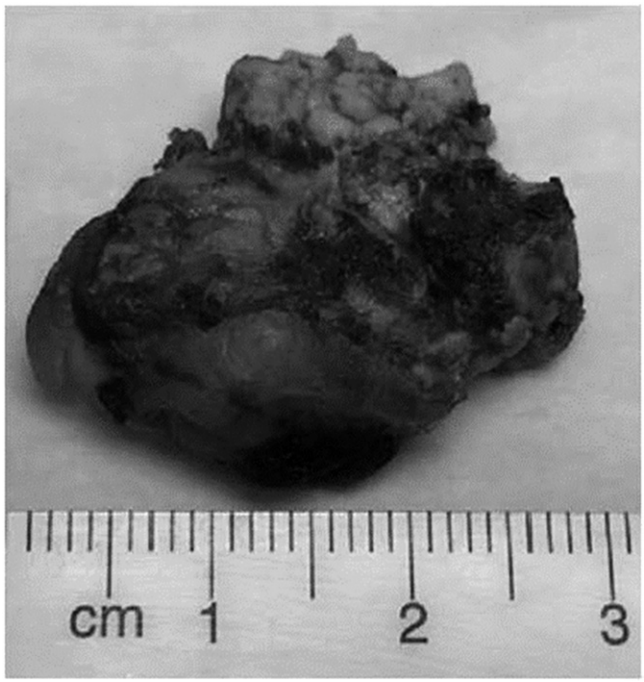

Fig. 2. Gross surgical specimen (distal pancreatectomy).

MSD discussing benign neoplasms is applicable to untreated insulinoma.

The U.S. Army aeromedical waiver guide addresses fasting hypoglycemia. Symptomatic hypoglycemia may be recommended for an aeromedical waiver if the underlying condition is controllable. A 72-h fast is recommended for diagnosis of fasting hypoglycemia and differentiation of underlying cause. In this patient's case, hypoglycemia was resolved with resection of insulinoma and required no ongoing therapy; therefore, a waiver could be considered for Army aeromedical personnel.[10] The U.S. Navy aeromedical waiver guide does not include a section for insulinoma or hypoglycemia.[7] The Federal Aviation Administration (FAA) addresses hypoglycemia, whether functional or a result of pancreatic tumor, in the endocrine section of the Guide for Aviation Medical Examiners. All medical records and current treatment regimen must be submitted, and this requires an FAA decision. In the case of hypoglycemia caused by insulinoma, resolved with surgical resection and requiring no medications, FAA waiver would be likely.[2]

After resection of the insulinoma, the patient's symptoms resolved with normal morning and fasting plasma glucose. He follows up with you in clinic and wants to know when he can return to flying status.

5. What is the most likely aeromedical disposition of this pilot?

A. Return to flight status after an observational period given no recurrence of hypoglycemia.
B. Recommend a permanent disqualification.
C. Submit a waiver.
D. Medical Evaluation Board.

ANSWER/DISCUSSION

5. C. Submitting a waiver for this condition is the correct next step. The patient is an instructor pilot, currently assigned to the T-6 airframe. It is important to consider the potential impact of hypoglycemia while flying alone or with a single copilot who may not be a fully trained pilot. However, in the case of insulinoma, surgical removal is almost always curative with a very low rate of recurrence, especially if the patient has been euglycemic for 6 mo postoperatively.

The patient's waiver was submitted and he was granted a Flying Class II waiver. This referenced MSD sections M30 and O2. After surgery, the patient's hypoglycemia resolved, the benign neoplasm was appropriately treated, and he does not require specialist evaluation annually. Per the patient's waiver determination, semiannual monitoring of fasting blood sugar was recommended with hemoglobin A1C testing to be performed at the discretion of the flight surgeon. Follow-up and surveillance per the National Comprehensive Cancer Network guidelines were also recommended.[4] The insulinoma National Comprehensive Cancer Network guidelines recommend checking biochemical markers at 3–12 mo postoperatively and then annually for up to 10 yr. Repeat imaging is recommended as clinically indicated but is not routinely recommended. The patient's endocrinologist recommended laboratory evaluation based on clinical symptoms, but no routine specialist follow-up was recommended or required. The patient has no duty or world-wide deployment restrictions recommended.

Repeat imaging performed 1 yr after surgery showed no evidence of disease recurrence. The patient has not experienced hypoglycemia or any symptoms suggestive of hypoglycemia.

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