

CASE REPORT WITH REVIEW OF LITERATURE

Ventricular fibrillation triggered by recurrent hypoglycemia in a patient with insulinoma associated with MEN1: case report and review of literature

Kotaro Doi¹⁾ , Shin Kaneko¹⁾, Yoshikuni Asami¹⁾, Amane Yamamoto²⁾ , Takeshi Kano³⁾, Yoshikuni Kawaguchi³⁾ , Kiyoshi Hasegawa³⁾ , Masafumi Kaiume⁴⁾ , Toshiko Kobori¹⁾ , Maki Takeuchi¹⁾ , Junichiro Sato¹⁾ , Midori Fujisihro⁵⁾ , Masaomi Nangaku¹⁾  and Noriko Makita¹⁾ 

¹⁾ Department of Nephrology and Endocrinology, The University of Tokyo Hospital, Tokyo 113-8655, Japan

²⁾ Department of Pathology, The University of Tokyo Hospital, Tokyo 113-8655, Japan

³⁾ Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, The University of Tokyo Hospital, Tokyo 113-8655, Japan

⁴⁾ Department of Radiology, The University of Tokyo Hospital, Tokyo 113-8655, Japan

⁵⁾ Center for Treatment of Diabetes & Obesity Disease, Nihon University Hospital, Tokyo 101-8309, Japan

Abstract. This report describes the case of a 44-year-old woman without structural heart disease who developed ventricular fibrillation (VF) during preoperative management of multiple pancreatic neuroendocrine tumors (NETs) associated with multiple endocrine neoplasia type 1. She had an insulinoma in the uncinate process and a non-functioning NET in the pancreatic tail. Immediately after intravenous glucose administration for recurrent hypoglycemia, VF occurred. An electrocardiogram obtained immediately before VF onset showed repolarization abnormalities with marked QTc prolongation, terminal T-wave bulging, and U waves. Laboratory testing revealed concomitant mild hypokalemia. No coronary artery disease was detected. The severe repolarization abnormalities improved after resection of the insulinoma. The presumed mechanism was that mild hypokalemia and recurrent hypoglycemia, together with hypoglycemia-induced epinephrine surge and extracellular-to-intracellular potassium shift, synergistically prolonged the action potential duration and induced early afterdepolarizations, which progressed from torsades de pointes to VF. This case highlights that unstable glycemic control in insulinoma can precipitate life-threatening arrhythmias, even in the absence of structural heart disease. Particularly when surgery is delayed, maintaining serum potassium as 4.5–5.0 mmol/L and preventing recurrent hypoglycemia are crucially important. Early recognition and intervention might help reduce arrhythmic risk in such patients.

Key words: Hypoglycemia, Hypokalemia, Insulinoma, MEN1, Ventricular fibrillation (VF)

Introduction

Insulin-induced hypoglycemia can trigger lethal arrhythmias, including sustained ventricular tachycardia and ventricular fibrillation (VF), leading to sudden cardiac death [1, 2]. This arrhythmogenic risk has been proposed as one contributor to the excess mortality which has been observed with intensive glycemic control in type 2 diabetes. However, most reported events have occurred in patients with diabetes who also have structural heart

disease or some other cardiometabolic comorbidity [3–5]. By contrast, reports of insulin-triggered hypoglycemia provoking VF in individuals without diabetes are exceedingly rare.

Herein, we report a case of VF in a 44-year-old woman with no prior structural heart disease. She was diagnosed with multiple pancreatic neuroendocrine tumors (NETs) associated with multiple endocrine neoplasia type 1 (MEN1): an insulinoma in the uncinate process and a nonfunctioning tumor in the tail of the pancreas. During the waiting period for pancreaticoduodenectomy, VF occurred, triggered by a relapse of hypoglycemia that had improved initially. No other identifiable cause of VF was found except for mild hypokalemia (serum potassium 3.3 mmol/L) and a prolonged QTc interval, suggesting that a relative catecholamine excess caused by recurrent

Submitted Oct. 16, 2025; Accepted Dec. 23, 2025 as EJ25-0494

Released online in J-STAGE as advance publication Feb. 17, 2026

Correspondence to: Noriko Makita, MD, PhD, Division of Nephrology and Endocrinology, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.

E-mail: norimakitky@gmail.com

hypoglycemia played a key role.

Findings from this case suggest that relapse of hypoglycemia, transitioning from an asymptomatic phase to a symptomatic state accompanied by excessive epinephrine secretion, can induce life-threatening arrhythmia even in the absence of structural heart disease, underscoring the importance of strict serum potassium control to 4.5–5.0 mmol/L in patients with insulinoma.

Case Presentation

A 44-year-old woman presented with impaired consciousness. She had noticed gradual weight gain during the preceding six months and had experienced transient episodes of early morning loss of consciousness starting three months prior. She experienced no noticeable hypoglycemic symptom such as sweating, palpitations, or tremors before admission. She was brought to the emergency department in a comatose state, where laboratory testing revealed severe hypoglycemia, with a blood glucose level of 19 mg/dL. Despite the hypoglycemia, serum immunoreactive insulin (IRI) was 6.3 μ U/mL; also, C-peptide (CPR) was 1.53 ng/mL. Both findings raised suspicion of insulinoma and prompted hospitalization for additional evaluation. She had no relevant family history.

On admission, physical examination was unremarkable. Blood tests revealed secondary hyperparathyroidism, presumably caused by vitamin D deficiency, whereas serum calcium levels remained within the normal range. Iron deficiency anemia was also observed, but the absence of symptoms of gastroesophageal reflux or melena led to a gynecological diagnosis of uterine polyp bleeding as the underlying cause (Table 1). Contrast-enhanced CT revealed a 26-mm hyperenhancing mass in the uncinate process of the pancreas during the arterial phase (yellow arrowhead, Fig. 1a). In addition to the lesion in the uncinate process detected on CT, non-contrast MRI revealed a 13-mm

Table 1 Blood test results at the time of admission

Biochemistry		Hematology	
TP	6.4 g/dL	WBC	4,600/ μ L
Alb	3.5 g/dL	Hb	9.4 g/dL
T.Bil	0.2 mg/dL	MCV	83.7 fL
AST	21 U/L	Plt	26.9 $\times 10^4$ / μ L
ALT	23 U/L	Glucose metabolism	
BUN	9.7 mg/dL	FPG	82 mg/dL
Cre	0.68 mg/dL	IRI	10.2 μ U/mL
eGFR	73.8 mL/min/1.73 m ²	CPR	2.4 ng/mL
Na	138 mmol/L	HOMA-IR	2.1
K	4.5 mmol/L	HOMA- β	193.3
Cl	105 mmol/L	HbA1c	4.4%
cCa	8.1 mg/dL	Endocrinology	
IP	1.6 mg/dL	ACTH	24.91 pg/mL
Mg	2.0 mg/dL	Cortisol	7.1 μ g/dL
CRP	0.14 mg/dL	Intact PTH	101 pg/mL
		25(OH)D	7.7 ng/mL

Abbreviations: TP, total protein; Alb, albumin; T.Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Cre, creatinine; eGFR, estimated glomerular filtration rate; Na, sodium; K, potassium; Cl, chloride; cCa, corrected calcium; IP, inorganic phosphate; Mg, magnesium; CRP, C-reactive protein; WBC, white blood cell count; Hb, hemoglobin; MCV, mean corpuscular volume; Plt, platelet count; FPG, fasting plasma glucose; IRI, immunoreactive insulin; CPR, C-peptide immunoreactivity; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA- β , homeostasis model assessment of β -cell function; HbA1c, hemoglobin A1c; ACTH, adrenocorticotrophic hormone; Cortisol, serum cortisol; Intact PTH, intact parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D

hyperintense mass in the pancreatic tail on T1-weighted imaging, suggesting either an accessory spleen or a tumor of the pancreatic tail (yellow arrowhead, Fig. 1b).

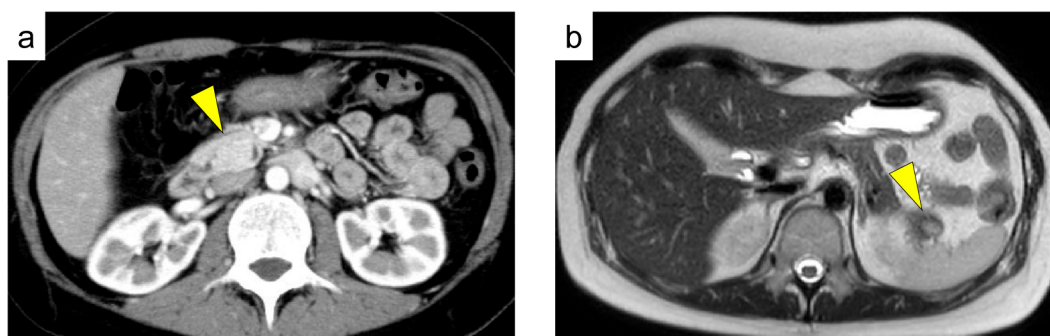


Fig. 1 Imaging features of pancreatic tumors

- A 26-mm hyperenhancing mass was observed in the uncinate process of the pancreas during the early contrast phase (yellow arrowhead).
- A 13-mm hyperintense mass on T2-weighted imaging was identified in the pancreatic tail (yellow arrowhead).

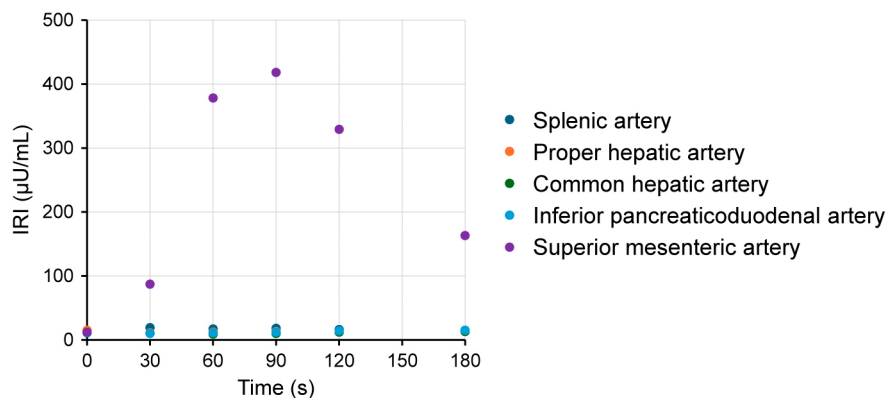


Fig. 2 Results of the selective arterial calcium injection (SACI) test

During the SACI testing, calcium injection into the superior mesenteric artery caused an increase in immunoreactive insulin (IRI) concentrations 30 s to 90 s after injection, although no such increase was observed with injections into other arteries.

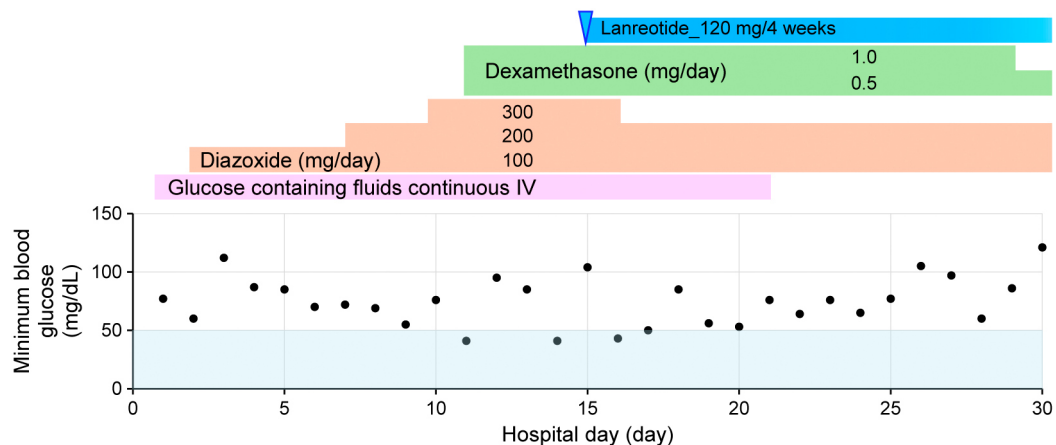


Fig. 3 Clinical course of glycemic management

For localization of the insulinoma, the selective arterial calcium injection (SACI) test showed an increase in immunoreactive insulin (IRI) concentrations 30 s–90 s after calcium injection into the superior mesenteric artery, with no response observed from other arteries (Fig. 2). Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was performed for both the uncinate process and tail lesions of the pancreas. Then they were diagnosed histologically as NETs. Immunohistochemical analysis revealed both tumors as positive for CD56, chromogranin A, and synaptophysin. The patient exhibited no symptoms of diarrhea. Upper gastrointestinal endoscopy revealed no evidence of peptic ulcers. Based on these findings, the lesion in the uncinate process was diagnosed as an insulinoma, whereas the lesion in the pancreatic tail was diagnosed as a nonfunctioning NET.

Management of hypoglycemia included diazoxide, which was limited to 200 mg/day because of severe nausea. Continuous intravenous glucose infusion, oral dexamethasone (0.5–1.0 mg/day), and long-acting somatostatin analog

lanreotide (120 mg every 4 weeks, subcutaneously) were administered. Following lanreotide initiation, hypoglycemic episodes decreased in frequency. Glucose infusion was discontinued (Fig. 3).

Given the presence of multiple pancreatic NETs, MEN1 was suspected. However, cervical ultrasound and pituitary MRI showed no evidence of parathyroid or pituitary tumors. Genetic testing for MEN1 was performed to guide surgical management of the pancreatic tail lesion. With stable glycemic control achieved by administration of dexamethasone and lanreotide, the patient was discharged on hospital day 30.

On day 24 after initiating lanreotide, the patient presented to the emergency department because of frequent episodes of undetectable glucose levels by the continuous glucose monitoring system, which did not improve with oral carbohydrate intake. Her blood glucose level on arrival was 48 mg/dL, prompting urgent hospitalization. A 7% glucose infusion was started. However, shortly thereafter, she developed sudden-onset impaired

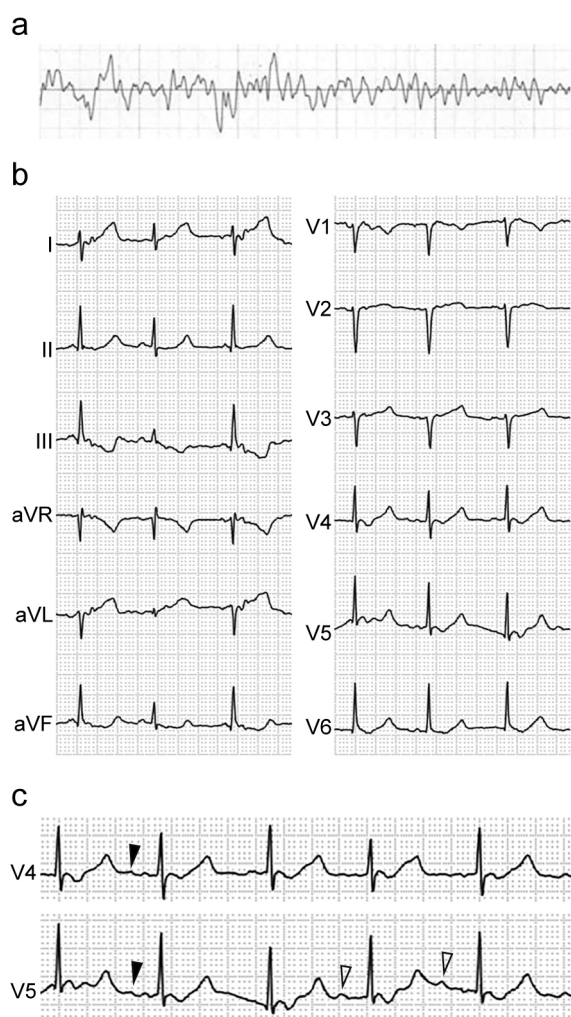


Fig. 4 12-lead ECG before onset of ventricular fibrillation on hospital day 40

- a. Representative ECG tracing showing VF at the time of loss of consciousness.
 b. 12-lead ECG before onset of VF.
 c. Terminal T-wave bulging and U wave on the ECG before VF onset: terminal T-wave bulging (black arrowheads) and U wave (white arrowheads).

consciousness attributable to VF (Fig. 4a). Return of spontaneous circulation was achieved after 4 min of cardiopulmonary resuscitation, including one defibrillation. Echocardiography revealed severely reduced left ventricular ejection fraction (LVEF) of approximately 10%, accompanied by global hypokinesis.

To aid in identifying the cause of VF, laboratory data obtained immediately before the event revealed mild hypokalemia and hypophosphatemia (Table 2). Electrocardiogram (ECG) showed marked QT interval prolongation (QTc 0.580/0.560 s, Fig. 4b, Table 3) together with repolarization abnormalities, including terminal T-wave bulging and U waves (Fig. 4c). Coronary angiography showed no

Table 2 Blood test results at the time of VF onset

Biochemistry	
Alb	4.0 g/dL
AST	56 U/L
ALT	88 U/L
LDH	247 U/L
CPK	72 U/L
BUN	12.1 mg/dL
Cre	0.78 mg/dL
Na	141 mmol/L
K	3.3 mmol/L
Cl	106 mmol/L
Ca	9.1 mg/dL
IP	1.8 mg/dL
Mg	1.9 mg/dL
CRP	0.09 mg/dL
Hematology	
WBC	5,200 / μ L
Hb	12.0 g/dL
Coagulation system	
D-dimer	2.1 μ g/mL

Abbreviations: Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; BUN, blood urea nitrogen; Cre, creatinine; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; IP, inorganic phosphate; Mg, magnesium; CRP, C-reactive protein; WBC, white blood cell count; Hb, hemoglobin; D-dimer, cross-linked fibrin degradation product

Table 3 QTc interval, blood glucose, and serum potassium levels throughout the clinical course

Date	QTc (s)	FPG (mg/dL)	sK (mmol/L)
-16	0.508/0.489	19	3.9
0	0.470/0.447	82	4.5
40	0.580/0.560	48	3.3
105 *	0.415/0.405	106	4.9

QTc were derived using Bazett's formula ($QTc = QT/\sqrt{RR}$) or Fridericia's formula ($QTc = QT/RR^{1/3}$), as appropriate.

Abbreviations: Date, hospitalization days based on the transfer date to our hospital; QTc, corrected QT interval; FPG, fasting plasma glucose; sK, serum potassium; *, after insulinoma removal

coronary artery disease. Mechanical circulatory support with veno-arterial extracorporeal membrane oxygenation and intra-aortic balloon pump was administered for three days, after which gradual recovery of LVEF was observed.

Subsequently, a pathogenic variant of the *MEN1* gene (c.1096G>T, p.Glu366*) was identified. The patient underwent robotic pancreatoduodenectomy. According to the Clinical Practice Guidelines for Gastroenteropancreatic

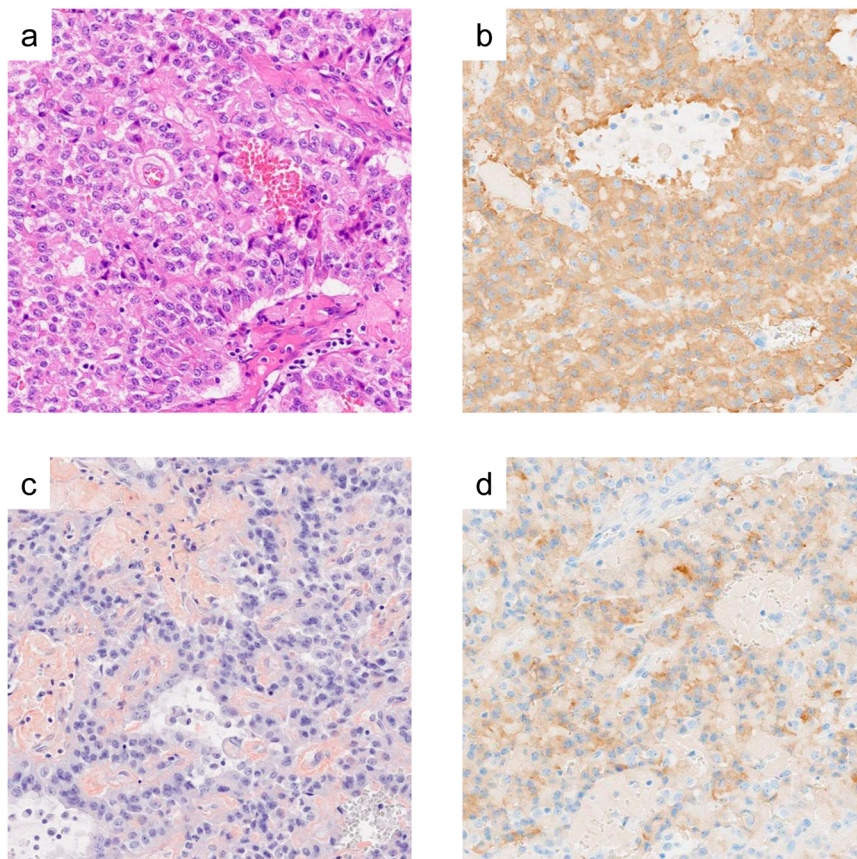


Fig. 5 Histopathological findings of the insulinoma in pancreatic uncinate process

- a. Hematoxylin and eosin staining ($\times 200$) reveals NET typical morphology. Tumor cells with round nuclei with salt and pepper chromatin and eosinophilic granular cytoplasm are proliferating in a trabecular pattern.
- b. Synaptophysin staining ($\times 200$).
- c. Direct Fast Scarlet staining revealed amyloid deposition in the tumor stroma, which is characteristic of insulinoma ($\times 200$).
- d. Insulin staining ($\times 200$).

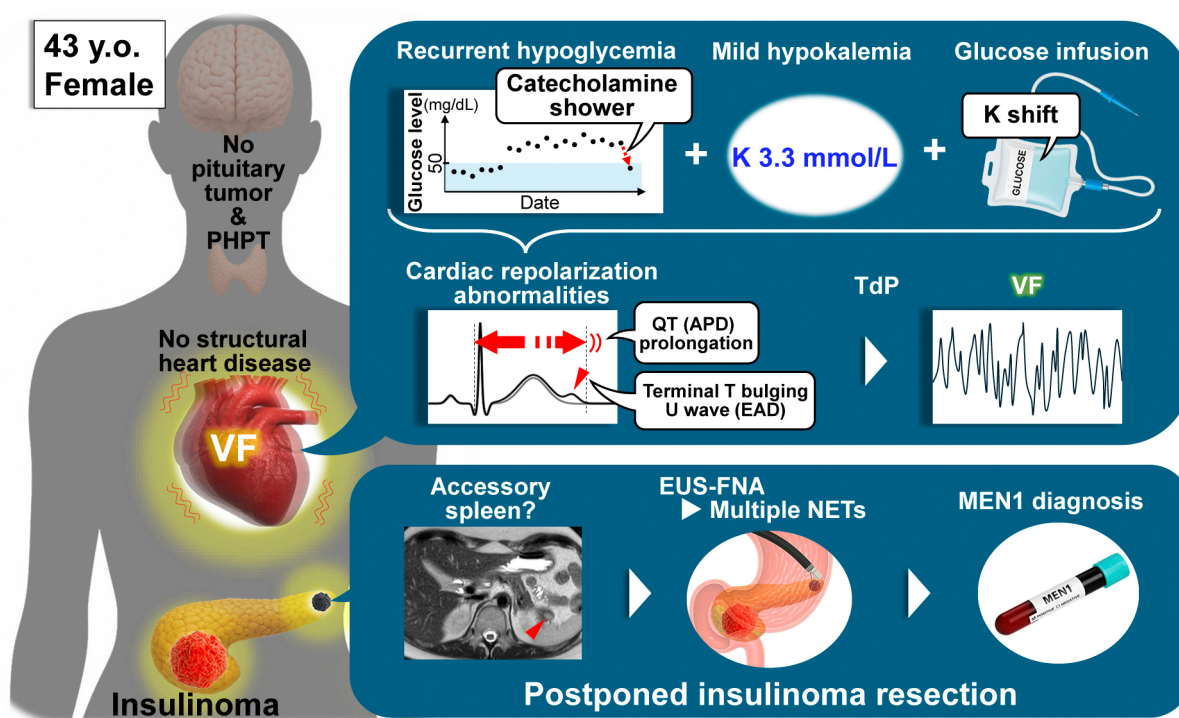
Neuroendocrine Neoplasm 2019 [6], the non-functioning lesion at the tail was not resected. In the surgical specimen, the tumor in the uncinate process of the pancreas was revealed as a solid nodule of $25 \times 24 \times 16$ mm. Histological assessment and immunohistochemistry of synaptophysin and insulin confirmed the tumor as insulinoma. The tumor was graded as G2 based on Ki-67 labeling index of 3%. Immunohistochemistry of somatostatin receptor 2 was also positive (not shown) (Fig. 5). In addition, a discontinuous 5×3 mm grade 1 NET, which was undetectable from preoperative imaging, was identified adjacent to the main lesion. Following resection of the insulinoma, the patient's hypoglycemic symptoms resolved. No recurrence of QT prolongation has been observed.

Discussion

In this case, a patient with multiple pancreatic NETs, an insulinoma in the uncinate process, and a nonfunctioning NET in the pancreatic tail arising in the context of

MEN1 developed VF immediately after glucose administration for recurrent, refractory hypoglycemia during the preoperative waiting period. Laboratory testing, echocardiography, and coronary angiography revealed no evidence of structural heart disease. However, mild hypokalemia and hypoglycemia were present. The ECG showed marked QT prolongation, terminal T-wave bulging, and U waves: findings strongly suggestive of severe myocardial repolarization abnormalities. Importantly, these severe repolarization abnormalities were observed only immediately before VF onset. They were absent after resection of the insulinoma. Taken together, these findings indicate that the principal mechanism underlying VF in this patient was reversible, severe myocardial repolarization abnormality (Graphical Abstract).

Reports of diagnostic insulin tolerance tests in humans describe a decline in blood glucose accompanied by a decrease in serum potassium of approximately 0.7 mmol/L before and after insulin administration, together with QTc prolongation, a rise in heart rate, and increased



Graphical Abstract Abbreviations: PHPT, primary hyperparathyroidism; VF, ventricular fibrillation; APD, action potential duration; EAD, early afterdepolarization; TdP, torsades de pointes; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; NET, neuroendocrine tumor

plasma epinephrine concentration [2]. Similar phenomena have also been reported from experimentation with insulin-induced hypoglycemia in rats, in which lethal arrhythmias such as ventricular tachycardia and third-degree atrioventricular block, as well as death, were documented [1].

Hypokalemia is known to impair various cardiac ion channels, including the human ether-a-go-go-related gene (hERG) potassium channel, initially causing prolonged action potential duration (APD) and subsequently leading to early afterdepolarizations (EADs) as the condition worsens. These cellular abnormalities manifest on the ECG as QT prolongation, terminal T-wave bulging, and U waves [7-12]. With regard to hypoglycemia, *in vitro* experiments demonstrated that reduced extracellular glucose directly impairs hERG channel function *per se*, providing a mechanistic link to QT prolongation [13]. Furthermore, excess epinephrine has been shown to aggravate this substrate. In fact, in the setting of pre-existing QT prolongation, β -adrenergic stimulation enhances L-type calcium channel activity, thereby triggering EADs and amplifying repolarization abnormalities [14-16].

Immediately before the onset of VF in this case, the patient's blood glucose concentration was 48 mg/dL. Her serum potassium concentration was 3.3 mmol/L. Although each abnormality was only mild when considered indi-

vidually, their coexistence is known to provoke QT prolongation [17]. Moreover, terminal T-wave bulging and U waves were observed exclusively on the ECG recorded immediately before VF onset, suggesting that EADs had occurred at that time [14]. Several reports have described that coexistence of QT prolongation and EADs amplifies repolarization abnormalities [18, 19]. Therefore, in this case, the combination of mild hypoglycemia, mild hypokalemia, and clinically suspected excess epinephrine secretion induced by recurrent hypoglycemia likely acted synergistically to produce severe QT prolongation (QTc 0.580/0.560 s). Critically, studies of diagnostic insulin tolerance tests in humans have reported reduction in serum potassium of approximately 0.7 mmol/L because of a transcellular shift following insulin administration [2]. This finding suggests that intravenous glucose infusion before VF onset might have lowered the serum potassium concentration further below 3.3 mmol/L, likely resulting in moderate or greater hypokalemia. Such aggravation of hypokalemia would have simultaneously worsened both the prolonged APD and facilitated EADs, ultimately promoting the transition from torsades de pointes to VF through these compound repolarization abnormalities [11].

On the ECG recorded at the referring hospital 16 days before admission to our institution, QT prolongation

(QTc 0.508/0.489 s) was noted, but no life-threatening arrhythmia occurred. At that time, severe hypoglycemia with a blood glucose concentration of 19 mg/dL likely induced QT prolongation through hERG potassium channel dysfunction [13]. However, because hypokalemia was absent and because no terminal T-wave bulging or U wave was observed, epinephrine-induced EADs were less likely to have developed (Supplementary Fig. 1a). Consequently, the repolarization abnormality did not progress to a severe degree.

In this case, biochemical evidence of epinephrine excess was not obtained immediately before VF onset. With insulinoma, however, repeated episodes of hypoglycemia can engender hypoglycemia unawareness, characterized by impaired epinephrine response [20]. Hypoglycemia unawareness is reversible. In fact, several days of therapeutic intervention to avoid hypoglycemia can restore counter-regulatory epinephrine secretion [21]. Tolerance to diazoxide in this patient was markedly poor because of nausea. Moreover, glycemic control was difficult, necessitating combined use of dexamethasone and lanreotide. After lanreotide administration, hypoglycemia was prevented for approximately three weeks, during which hypoglycemia unawareness was likely ameliorated. However, hypoglycemia recurrence happened once the effect of lanreotide had worn off, before the next scheduled dose. This clinical course, transitioning from hypoglycemia unawareness to symptomatic hypoglycemia, suggests that recurrent hypoglycemia immediately before VF was sufficient to provoke epinephrine excess [21]. Furthermore, the terminal T-wave bulging and U waves, which were findings suggestive of EADs, were observed only on the hospital day 40 ECG (Supplementary Fig. 1a–d). The T wave bulging and U waves are most likely attributable to epinephrine excess, given that QT prolongation could already be induced under conditions of mild hypoglycemia and mild hypokalemia [14].

Thirumalai *et al.* reported a case of VF in a 33-year-old woman with insulinoma, in whom LVEF improved after tumor resection. In that case, it remained unclear whether serum potassium levels or QT prolongation were present at the time of VF, but because the LVEF persisted in the 20% range and an implantable cardioverter-defibrillator was subsequently placed, the authors concluded that an underlying dilated cardiomyopathy was present [22]. By contrast, the VF in our case occurred in the absence of structural heart disease. After insulinoma resection, the reversible acquired long QT syndrome resolved. Therefore, rather than by any structural cardiac disorder, we consider that VF in our patient was triggered by severe myocardial repolarization abnormality, as described above, induced by recurrent hypoglycemia in combination with hypokalemia that worsened from mild

to moderate severity following glucose infusion.

Early surgical resection of insulinoma is the most effective intervention for preventing VF associated with insulinoma-induced hypoglycemia. In the case described herein, VF occurred during the preoperative waiting period, which extended to three months. The delay was largely attributable to the need for MEN1 genetic testing to ascertain whether the non-functioning pancreatic NET in the tail, as diagnosed by imaging and pathology, should be resected at the time of insulinoma surgery [23]. Primary hyperparathyroidism (PHPT), which develops before other NETs in over 95% of patients with MEN1, has been reported to manifest in more than 85% of individuals by the age of 25 [24]. By contrast, cases similar to that described herein have also been reported, in which patients with MEN1 develop multiple pancreatic NETs in their 40s without evidence of PHPT [25]. Consequently, the process of evaluating whether MEN1 genetic testing was warranted based solely on the presence of multiple pancreatic NETs, in the absence of PHPT, also contributed to the delay in surgical intervention.

A target serum potassium level of 4.5–5.0 mmol/L is recommended for patients with QT prolongation syndrome [26]. Additionally, an animal study using a rat model of hypoglycemia-induced arrhythmia demonstrated that potassium supplementation significantly reduced the incidence of lethal arrhythmic events [1]. In the context of insulin-induced hypoglycemia, management of lethal arrhythmia risk might be more straightforward in diabetic patients with underlying structural heart disease because the irreversible characteristics of their cardiac condition often promote consistent awareness and adherence to serum potassium control [27]. By contrast, as the present case illustrates, patients with insulinoma might exhibit reversible QT prolongation depending on the quality of glycemic control, which can fluctuate over time. This variation might obscure recognition of the importance of potassium management in such patients. As particularly suggested by the present case, a clinical scenario in which therapeutic interventions for hypoglycemia initially succeed but subsequently fail, leading eventually to recurrent hypoglycemia, should be recognized as a condition not of asymptomatic hypoglycemia but as one accompanied by excessive epinephrine secretion, which can exacerbate QT prolongation further. Lanreotide for insulinoma is typically administered subcutaneously every 4 weeks, yet this interval may prove insufficient in some patients [28]. When therapeutic efficacy wanes beyond the third week—as observed in our case—restoration of hypoglycemic awareness may paradoxically heighten arrhythmia risk through enhanced counter-regulatory epinephrine responses. Close inpatient glucose monitoring following each administration is therefore essential.

Our case highlights several important clinical considerations for insulinoma patients with prolonged surgical waiting periods or difficulty in achieving stable glycemic control: (1) serum potassium levels must be maintained at 4.5–5.0 mmol/L, (2) recurrent hypoglycemia must be prevented to mitigate risks of life-threatening arrhythmias, and (3) when lanreotide is administered, careful monitoring for recurrent hypoglycemia beyond the third week of treatment is warranted due to potential attenuation of therapeutic effect.

Consent to Publication

The patient provided consent for publication of this case study.

Disclosure

No author has any potential conflict of interest associ-

ated with this research. Noriko Makita is a member of *Endocrine Journal's* Editorial Board.

Funding

None to declare.

Author Contributions

Pathological diagnosis: A.Y.; Surgical treatment: Takeshi K., Y.K., and K.H.; Clinical diagnosis/treatment: K.D., S.K., Y.A., Toshiko K., M.K., M.T., J.S., and M.F.; Literature and data collection and review: K.D.; Writing – original draft preparation: K.D.; Writing – review and editing: K.D., M.N., and N.M.; Supervision: M.N. and N.M. All authors reviewed and approved the final version of the manuscript for publication.

References

1. Reno CM, Daphna-Iken D, Chen YS, VanderWeele J, Jethi K, *et al.* (2013) Severe hypoglycemia-induced lethal cardiac arrhythmias are mediated by sympathoadrenal activation. *Diabetes* 62: 3570–3581.
2. Kacheva S, Karges B, Göller K, Marx N, Mischke K, *et al.* (2017) QT prolongation caused by insulin-induced hypoglycaemia—an interventional study in 119 individuals. *Diabetes Res Clin Pract* 123: 165–172.
3. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC, Jr, *et al.* (2008) Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358: 2545–2559.
4. Stahn A, Pistrosch F, Ganz X, Teige M, Koehler C, *et al.* (2014) Relationship between hypoglycemic episodes and ventricular arrhythmias in patients with type 2 diabetes and cardiovascular diseases: silent hypoglycemia and silent arrhythmias. *Diabetes Care* 37: 516–520.
5. Chow E, Bernjak A, Williams S, Fawdry RA, Hibbert S, *et al.* (2014) Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. *Diabetes* 63: 1738–1747.
6. Ito T, Masui T, Komoto I, Doi R, Osamura RY, *et al.* (2021) JNETS clinical practice guidelines for gastroenteropancreatic neuroendocrine neoplasms: diagnosis, treatment, and follow-up: a synopsis. *J Gastroenterol* 56: 1033–1044.
7. Massaelli H, Guo J, Xu J, Zhang S (2010) Extracellular K⁺ is a prerequisite for the function and plasma membrane stability of HERG channels. *Circ Res* 106: 1072–1082.
8. Guo J, Massaelli H, Xu J, Jia Z, Wigle JT, *et al.* (2009) Extracellular K⁺ concentration controls cell surface density of IKr in rabbit hearts and of the HERG channel in human cell lines. *J Clin Invest* 119: 2745–2757.
9. Melgari D, Du C, El Harchi A, Zhang Y, Hancox JC (2014) Suppression of the hERG potassium channel response to premature stimulation by reduction in extracellular potassium concentration. *Physiol Rep* 2: e12165.
10. Weiss JN, Qu Z, Shivkumar K (2017) Electrophysiology of hypokalemia and hyperkalemia. *Circ Arrhythm Electrophysiol* 10: e004667.
11. Pezhouman A, Singh N, Song Z, Nivala M, Eskandari A, *et al.* (2015) Molecular basis of hypokalemia-induced ventricular fibrillation. *Circulation* 132: 1528–1537.
12. Yan GX, Antzelevitch C (1998) Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. *Circulation* 98: 1928–1936.
13. Zhang Y, Han H, Wang J, Wang H, Yang B, *et al.* (2003) Impairment of human ether-à-go-go-related gene (HERG) K⁺ channel function by hypoglycemia and hyperglycemia. Similar phenotypes but different mechanisms. *J Biol Chem* 278: 10417–10426.
14. Shimizu W, Antzelevitch C (1998) Cellular basis for the ECG features of the LQT1 form of the long-QT syndrome: effects of beta-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. *Circulation* 98: 2314–2322.
15. Ackerman MJ, Khositseth A, Tester DJ, Hejlik JB, Shen WK, *et al.* (2002) Epinephrine-induced QT interval prolongation: a gene-specific paradoxical response in congenital long QT syndrome. *Mayo Clin Proc* 77: 413–421.
16. Vyas H, Hejlik J, Ackerman MJ (2006) Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: diagnostic accuracy of the paradoxical QT

- response. *Circulation* 113: 1385–1392.
17. Kang MY (2015) Blood electrolyte disturbances during severe hypoglycemia in Korean patients with type 2 diabetes. *Korean J Intern Med* 30: 648–656.
 18. Yan GX, Wu Y, Liu T, Wang J, Marinchak RA, *et al.* (2001) Phase 2 early afterdepolarization as a trigger of polymorphic ventricular tachycardia in acquired long-QT syndrome: direct evidence from intracellular recordings in the intact left ventricular wall. *Circulation* 103: 2851–2856.
 19. Kurata Y, Tsumoto K, Hayashi K, Hisatome I, Kuda Y, *et al.* (2019) Multiple dynamical mechanisms of phase-2 early afterdepolarizations in a human ventricular myocyte model: involvement of spontaneous SR Ca (2+) release. *Front Physiol* 10: 1545.
 20. Abdelgadir A, Li Voon Chong J (2025) Atypical presentation of insulinoma in a patient with hypoglycemia unawareness: a case report. *Cureus* 17: e83789.
 21. Hölzen L, Schultes B, Meyhöfer SM, Meyhöfer S (2024) Hypoglycemia unawareness-a review on pathophysiology and clinical implications. *Biomedicines* 12: 391.
 22. Thirumalai A, Levander XA, Mookherjee S, White AA (2013) Insulinoma presenting with cardiac arrest and cardiomyopathy. *BMJ Case Rep* 2013: bcr2013009193.
 23. Sulciner ML, Clancy TE (2023) Surgical management of pancreatic neuroendocrine tumors. *Cancers (Basel)* 15: 2006.
 24. Mele C, Mencarelli M, Caputo M, Mai S, Pagano L, *et al.* (2020) Phenotypes associated with MEN1 syndrome: a focus on genotype-phenotype correlations. *Front Endocrinol (Lausanne)* 11: 591501.
 25. Horikoshi H, Arita J, Hasegawa K, Makita N (2023) A novel pathogenic MEN1 gene variant identified in a family with multiple pancreatic neuroendocrine tumors. *JCEM Case Rep* 1: luad078.
 26. Thomas SH, Behr ER (2016) Pharmacological treatment of acquired QT prolongation and torsades de pointes. *Br J Clin Pharmacol* 81: 420–427.
 27. Leon BM, Maddox TM (2015) Diabetes and cardiovascular disease: epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes* 6: 1246–1258.
 28. Howarth S, Ho TW, Wimbury J, Casey R (2025) Managing hypoglycaemia in patients with insulinoma-A tertiary centre experience and review of the literature. *Clin Endocrinol (Oxf)* 102: 344–354.