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Authors: Alicja Rajewska, Paweł Komarnicki, Adam Maciejewski, Jan Musiałkiewicz, Paweł Gut, Marek Ruchała

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Multidisciplinary management of severe refractory hypoglycemia

Alicja Rajewska[1], Paweł Komarnicki[1], Adam Maciejewski[1], Jan Musiałkiewicz[1], Paweł Gut[1], Marek Ruchała[1]

Department of Endocrinology, Metabolism, and Internal Diseases, Poznan University of Medical Sciences, Poznań, Poland

Correspondence to: Alicja Rajewska, MD, Department of Endocrinology, Metabolism, and Internal Diseases, Poznan University of Medical Sciences, ul. Przybyszewskiego 49, 60-355 Poznań, Poland, phone: +48 61 869 13 30, email: alicja.rajewska@usk.poznan.pl

We present a case of a 57-year-old woman with an insulin-secreting pancreatic neuroendocrine tumor (PanNET), who experienced recurrent episodes of severe hypoglycemia refractory to multiple lines of standard therapy. Insulinoma diagnosis is based on clinical presentation, biochemical evaluation, somatostatin receptor suppression testing, and imaging studies. Its clinical course may be unpredictable, and treatment may be challenging. [1,2]

The patient was admitted to the hospital with recurrent syncopal episodes in the course of hypoglycemia, with blood glucose levels dropping down to 35 mg/dL (reference range, 70-99 mg/dL). Serum insulin - 23.97μIU/mL (reference range 2-25μIU/mL) and C-peptide - 2.17 nmol/l (reference range, 0.37-1.2 nmol/l) were inappropriately elevated. Magnetic resonance imaging scan of the abdomen revealed liver metastases (Figure 1A). Extended imaging diagnostics, including fluorine-18 fluorodeoxyglucose positron emission tomography / computed tomography, confirmed a lesion in the pancreatic tail with metastases to regional lymph nodes and the liver (Figure 1B and 1C). The above results indicated metastatic

insulinoma. Subsequently, the patient underwent pancreatic tail resection. The histopathology report confirmed well-differentiated PanNET G2, with Ki67 of 3%. Shortly after surgery, the patient was readmitted to the hospital due to severe refractory hypoglycemia with deterioration of logical contact. We performed HYNIC-TOC-Tc 99m scintigraphy, which confirmed increased tracer uptake in the liver (Figure D). Due to the hormonally active, liver-metastatic lesions, treatment with long-acting octreotide (30 mg monthly) was initiated. As the treatment failed to prevent hypoglycemia, we qualified the patient for four cycles of 100 mCi of yttrium-90 DOTA-0-Tyr3-Octreotate (3.7 GBq/100 mCi), a peptide receptor radionuclide therapy (PRRT). PRRT resulted in symptomatic relief and normalization of blood glucose for an extended period of time. However, this therapy was followed by a decline in renal function and the patient ultimately developed chronic kidney disease, limiting the use of next systemic treatment options. The patient underwent two partial hepatectomies and eleven thermal ablation procedures between 2013 and 2024. In 2024, due to relapse of hypoglycemia episodes we initiated diazoxide therapy. As the dosage was increased to 75 mg, the patient exhibited symptoms of growing edema. Due to disease progression, we initiated pasireotide (40 mg monthly) (Figure E), which has been reported to improve hypoglycemia control in insulinomas. [3] One month after the second dose, the patient was admitted to Endocrinology Department due to recurrence of hypoglycemia. During hospitalization, 200µg of short-acting octreotide, 40 mg of verapamil and 10 mg of prednisone were administered. Due to poor glycemic control, the patient was ultimately qualified for chemoembolization with doxorubicin, which targeted the largest metastatic lesion in the liver (Figure 1F). Glycemic control was finally achieved (Figure G). The patient received maintenance therapy with 5mg everolimus daily and 120 mg of Lanreotide monthly. Hypoglycaemic episodes are currently sporadic and not severe. The patient monitors her blood glucose levels using the Continuous Glucose Monitoring System.

Our patient underwent almost all therapeutic options recommended in the treatment of insulinoma according to current European guidelines (Figure H). [4] Although metastatic insulinomas are rare, their therapeutic management is complicated and must take into account both symptom management and the control of tumor proliferation. Both surgical and systemic treatments need to be considered, with careful approach to both the order of treatment and precise selection.

Article information

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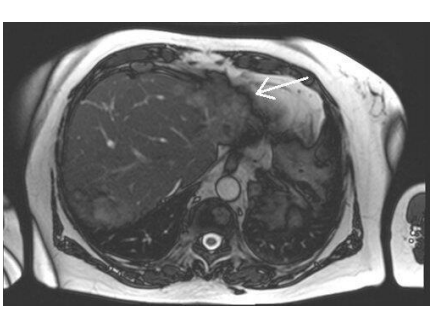

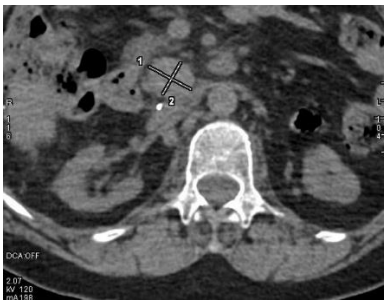

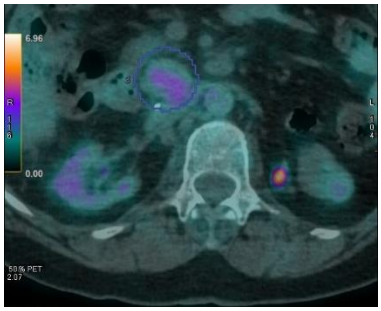

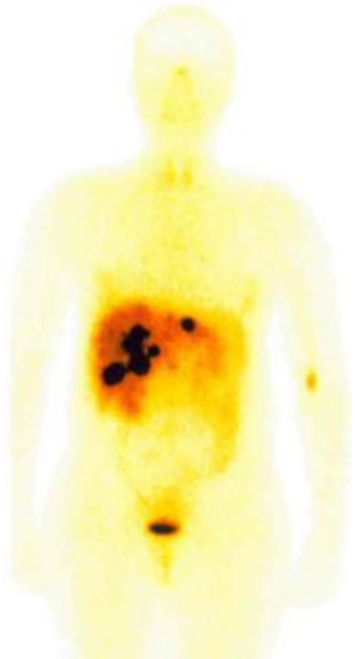

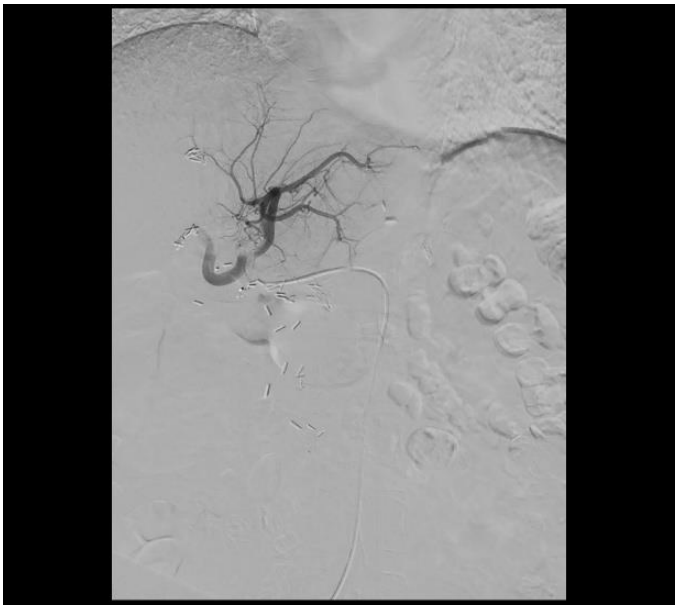

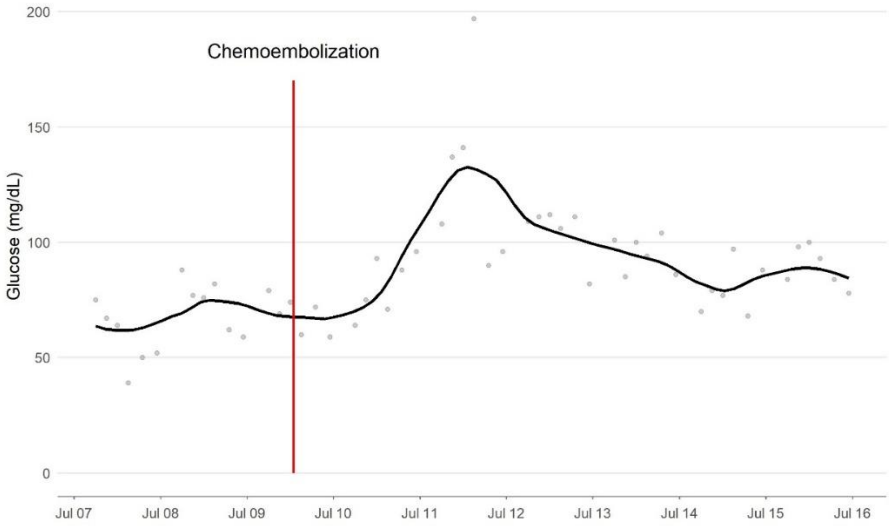

Clinical Timeline of Treatment Course

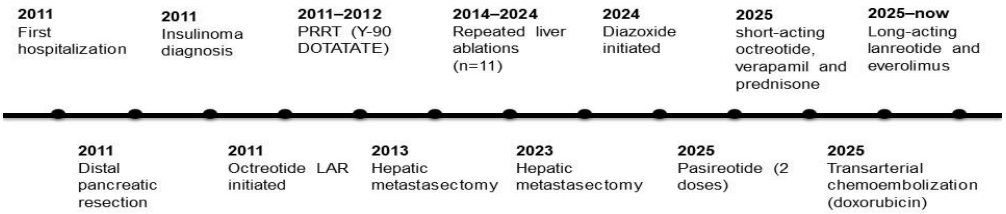

Figure 1 A – axial T2-weighted magnetic resonance image. In segments II and VII, ill-defined hyperintense areas in a subphrenic location are consistent with metastatic lesions originating from insulinoma; **B**, **C** – fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography / computed tomography images. In the area of the inferior vena cava, between the hepatic hilum and the renal vessels, there is a nodal mass with cross-sectional dimensions of 28 x 21 mm with increased uptake of ^{18}F-FDG (maximum standardized uptake value, 4.5); **D** – HYNIC-TOC-Tc99m whole-body scintigram 3 hours after intravenous administration of Tyr3-Octreotide. The scan confirms pathological uptake in the liver; **E** – ambulatory glucose profile (14 days) obtained from continuous glucose monitoring (FreeStyle Libre), recorded two weeks after initial intramuscular administration of pasireotide LAR (40 mg), demonstrating persistent hypoglycemia without clinically meaningful improvement; **F** – digital subtraction angiography during transarterial chemoembolization. The catheter is superselectively positioned in the proximal left hepatic artery, with opacification of the arterial vasculature of the left hepatic lobe. Surgical clips from prior laparotomies are also visible; **G** – blood glucose levels (mg/dL), measured at multiple time points between 7 and 16 July are shown as individual data points. A locally weighted regression curve (black line) was applied to visualize nonlinear temporal trends. The vertical red line indicates the time of chemoembolization (July 9, 15:00). Following the intervention, a delayed increase in glucose level is observed; **H** – clinical timeline of treatment course from 2011 to 2026

Short title: Effective insulinoma management