

## CASE REPORT

# Clinical remission of an inoperable malignant insulinoma by the combination treatment with octreotide and everolimus

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**Abstract**

We report a 52-year-old woman with inoperable malignant insulinoma with multiple liver metastases. Histological examination of biopsy specimens from the pancreatic and hepatic lesions revealed pancreatic neuroendocrine tumor (pNET), G2. The tumor cells were positive for somatostatin receptor (SSTR) 2, 5, and the mammalian target of rapamycin (mTOR). Monthly intramuscular administration of octreotide LAR and once-daily oral administration of everolimus combination treatment markedly reduced the sizes of liver metastases, and hypoglycemia was well controlled. Combination treatment with somatostatin analog and mTOR inhibitor may be another effective approach in inoperable metastatic malignant insulinoma.

**KEYWORDS**

everolimus, malignant insulinoma, mammalian target of rapamycin, multiple liver metastases, octreotide, somatostatin receptor

## 1 | INTRODUCTION

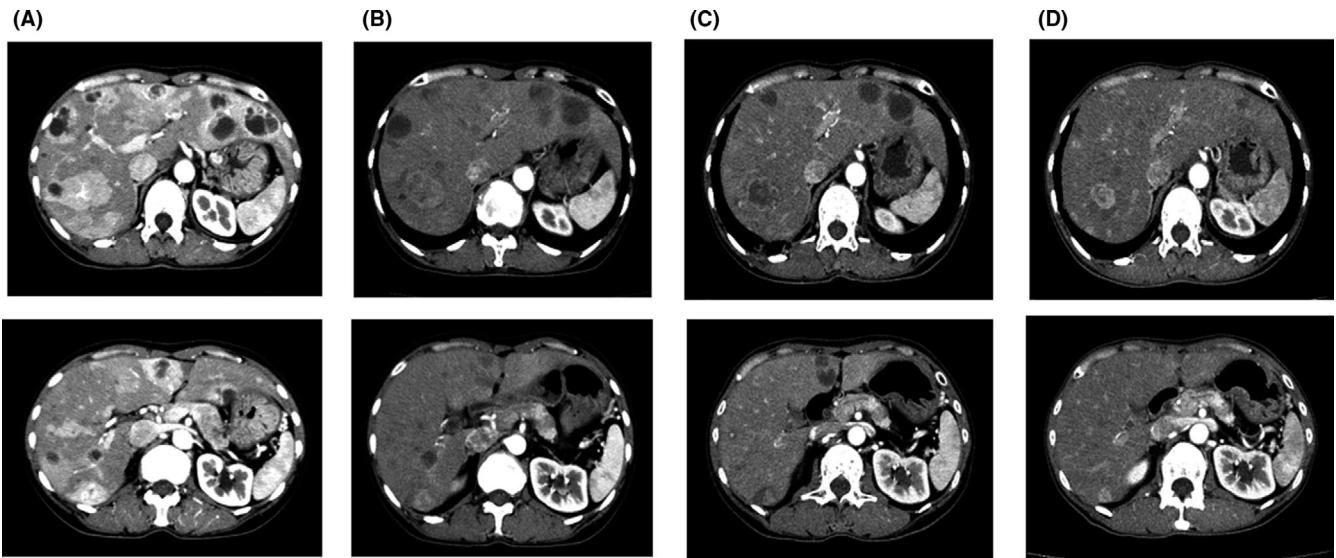
Insulinomas are insulin-producing tumors, which are usually benign solitary tumors. However, 10%-15% of insulinomas are malignant and may show an aggressive course with metastasis to the liver as well as more distant sites.<sup>1,2</sup> Medical therapy with somatostatin analog is indicated in patients with unresectable malignant insulinoma. However, evidence of an antitumor growth effect of somatostatin analog in pancreatic neuroendocrine tumors (pNET) is still lacking. Recently, the novel molecular-targeted therapeutic agent, everolimus, an orally active mammalian target of rapamycin (mTOR) inhibitor, has been shown to have antitumor growth effects in patients with pNET.<sup>3</sup> Here, we report a case of inoperable metastatic malignant insulinoma with marked reduction of liver metastases and good hypoglycemia control by monthly intramuscular administration of octreotide LAR and once-daily oral administration of everolimus.

## 2 | CASE REPORT

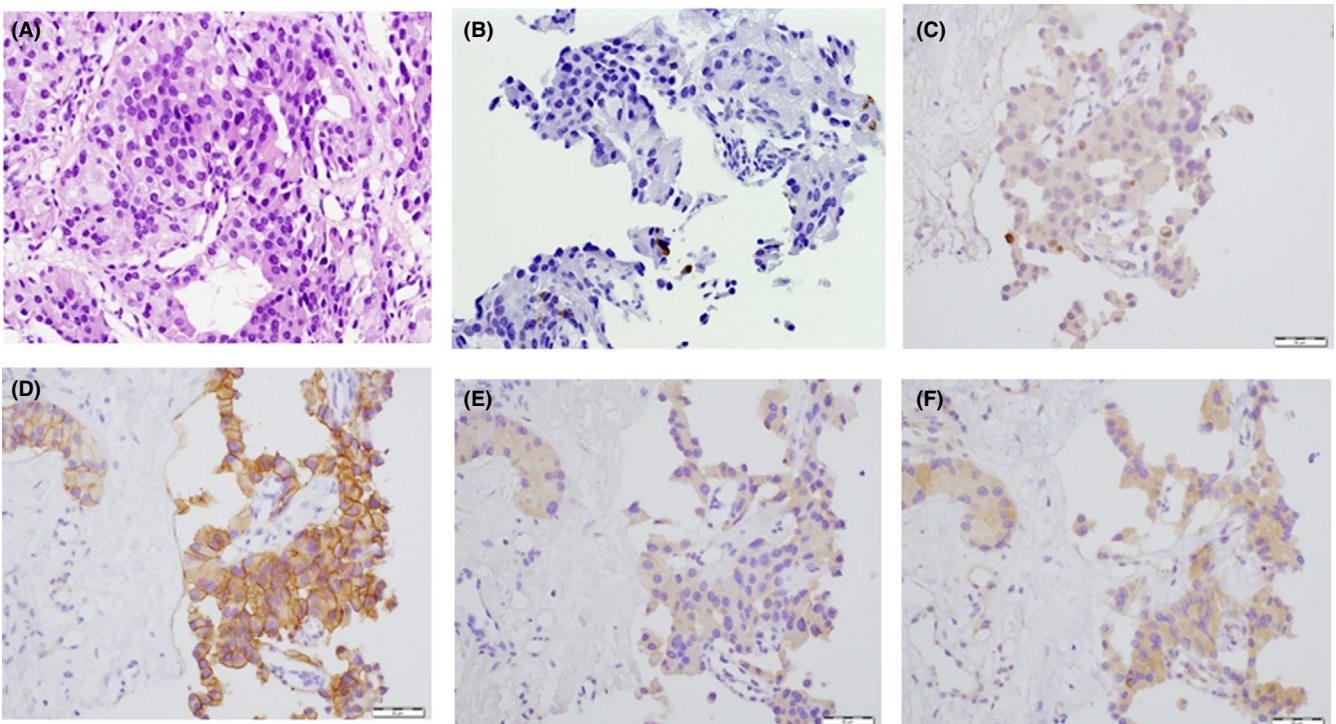
A 52-year-old woman was admitted to our hospital suffering from epigastric pain. She experienced several intermittent hypoglycemic episodes for over half a year. During admission, she presented with neurological symptoms of hypoglycemia. Her simultaneous plasma glucose level was 37 mg/dL with inappropriately high serum IRI level (45.8  $\mu$ IU/mL) and Fajan's index (IRI/plasma glucose) of 1.24 (normal, <0.30). ACTH and cortisol levels were within the respective normal ranges. Anti-insulin antibodies were negative. There was no history of use of hypoglycemic agents, alcohol abuse, or liver disease. Abdominal computed tomography (CT) demonstrated a 28-mm primary tumor in the tail of the pancreas with multiple lymph nodes, and multiple metastatic lesions in both lobes of the liver with the largest one 40 mm in diameter (Figure 1A). Endoscopic ultrasound fine needle aspiration cytology of pancreatic lesions and percutaneous liver core biopsies was performed. On histological examination,

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**FIGURE 1** Time course of changes in enhanced abdominal computed tomography (CT) findings on admission (A), 4 months (B), 10 months (C), and 20 months (D) after the treatment. An irregularly hypervascular tumor in the tail of the pancreas and multiple metastatic lesions were seen in both lobes of the liver was seen on admission



**FIGURE 2** Histopathological and immunohistochemical findings of specimens of liver metastases. The tumor cells formed monotonous solid areas with oval nuclei and eosinophilic cytoplasm, and had rare mitotic figures (H&E staining,  $\times 200$  magnification) (A). The tumor cells were positive for insulin (B), SSTR 2 (D), 5 (E), and phosphorylation of mTOR (F). They had a Ki-67 index of 6% (C) ( $\times 200$  magnification)

a consistent finding in all specimens was the presence of the tumor cells forming monotonous solid areas with oval nuclei and eosinophilic cytoplasm. There were rare mitotic figures (Figure 2A). On immunohistochemical analysis, the liver tumor cells were positive for chromogranin, synaptophysin and insulin, and showed a Ki-67 index of 6% (Figure 2B,C). Based on these findings, a diagnosis of

pancreatic neuroendocrine tumor (pNET), G2, with multiple liver metastases was made. Multiple endocrine neoplasia was excluded as no tumors were detected in the pituitary gland or parathyroid gland.

On 100  $\mu\text{g}$  octreotide loading test, plasma glucose was increased, while plasma IRI was decreased, suggesting that octreotide may be useful to control hypoglycemia. More than, we introduced

mTOR inhibitor in combination with octreotide treatment as a more reliable method for prevention of the tumor growth. Further immunohistochemical analysis showed that the tumor cells were positive for SSTR 2, 5 (especially strong membrane immunoreactivity for SSTR 2), and mTOR (Figure 2D-F). Based on these findings, we decided to perform subcutaneous injection of octreotide at a dose of 50 µg twice a day and prescribe everolimus, an inhibitor of mTOR, at 10 mg daily. Her plasma glucose levels improved, and there were no further hypoglycemic episodes. From 2 weeks after the treatment, we changed the treatment from daily subcutaneous injection of octreotide to monthly intramuscular injection of octreotide LAR, a long-acting octreotide formulation. Sequential changes in the pancreatic tumor and metastatic lesions of the liver on abdominal CT are shown in Figure 1. After 20 months of combination treatment with octreotide and everolimus, all of the metastatic lesions of the liver were reduced in size, and many of those had disappeared. In addition, swollen lymph nodes around the pancreatic tumor had also disappeared.

### 3 | DISCUSSION

Surgical resection is the first choice of therapy for benign and malignant insulinomas, where possible. However, medical therapy is indicated in patients with unresectable malignant insulinoma. In patients with NEC G1/G2, molecular-targeted treatment is recommended to decrease tumor growth progression. Moreover, medical therapy is required to control hypoglycemia due to insulin hypersecretion. Treatment to inhibit insulin hypersecretion includes the use of somatostatin analog or diazoxide. Somatostatin, a ubiquitous polypeptide, inhibits the secretion of many hormones including insulin, glucagon, growth hormone, and gastrin.<sup>4</sup> Octreotide and lanreotide bind mainly to SSTR subtypes 2 and 5, and less to SSTR subtype 3.<sup>5</sup> In insulinoma, the expression level of SSTR subtypes 2 and 5 is high, so the rate is about 70%.<sup>6</sup> Therefore, the patients with pNET positive for anti-SSTR2 immunostaining are responsive to somatostatin analog.<sup>7</sup> Octreotide has been reported to inhibit tumor growth in patients with midgut NETs (PROMID study).<sup>8</sup> Lanreotide has been also reported to have the effect of antitumor growth in pNETs (CLARINET study). Octreotide was used in our case, because octreotide is the only somatostatin analog that is used in functioning pNET at that time. However, antitumor effect of octreotide remains to be established in pNET including insulinoma.

Recently, everolimus, an orally active mammalian target of rapamycin (mTOR) inhibitor, has been shown to have antitumor growth effects in patients with pNET.<sup>3</sup> The protein of mTOR is a serine/threonine kinase that regulates cell growth, proliferation, and metabolism. In pNETs, the expression of mTOR protein is upregulated.<sup>9</sup> The expression and activity of mTOR and its downstream targets such as 4EBP1, S6, and eIF4E are strongly dependent on enhanced proliferative capacity and metastatic status in gastroenteropancreatic neuroendocrine foregut and midgut tumors. Evidence from preclinical studies suggests that the

combination of pasireotide and everolimus may be synergistic by dual inhibition of insulin-like growth factor-1 (IGF-1) and mTOR signaling.<sup>10</sup> The combination treatment may be more effective than each treatment. The maintenance therapy with somatostatin analog and mTOR inhibitor combination treatment may play a significant role in tumor control in patients with advanced NET, unless hyperglycemia induced. Further studies in larger numbers of insulinoma patients are required to support this suggestion.

### 4 | CONCLUSION

We reported a case of inoperable metastatic malignant insulinoma, in which liver metastases were markedly reduced and hypoglycemia was well controlled by monthly intramuscular administration of octreotide LAR and once-daily oral administration of everolimus. Combination treatment with somatostatin analog and mTOR inhibitor may be another effective approach in inoperable metastatic malignant insulinoma.

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### CONFLICT OF INTEREST

The author has stated explicitly that there are no conflicts of interest in connection with this article.

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