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CASE REPORT

High Intensity Focused Ultrasound Ablation of Pancreatic Neuroendocrine Tumours: Report of Two Cases

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Abstract We describe the use of ultrasound-guided high-intensity focused ultrasound (HIFU) for ablation of two pancreatic neuroendocrine tumours (NETs; insulinomas) in two inoperable young female patients. Both suffered from episodes of severe nightly hypoglycemia that was not efficiently controlled by medical treatment. After HIFU ablation, local disease control and symptom relief were achieved without postinterventional complications. The patients remained free of symptoms during 9-month follow-up. The lesions appeared to be decreased in volume, and there was decreased enhancing pattern in the multidetector computed tomography control (MDCT). HIFU is likely to be a valid alternative for symptoms control in patients with pancreatic NETs. However, currently the procedure should be reserved for inoperable patients for whom symptoms cannot be controlled by medical therapy.

Keywords Interventional Radiology · Interventional Oncology

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Introduction

The first choice therapy of neuroendocrine pancreatic tumours is surgical resection or enucleation [1]. In cases of patients with metastases or those with high surgical risk, the alternatives may be medical therapy [2], radiofrequency ablation (RFA) [3], or percutaneous embolization [4, 5].

High-intensity focused ultrasound (HIFU) has been recently introduced for the treatment of pancreatic cancer [6]. We report two patients in whom severe hypoglycemia caused by pancreatic insulinomas was controlled with the use of HIFU.

Case Report

Case No. 1: Clinical History

A 44-year-old woman had type II diabetes that had developed during her first pregnancy in 2003, which was controlled with oral therapy. Three years later, she developed severe nightly hypoglycemia (decreased glucose concentration of 36 mg/dl [2 mmol/dl]). Ultrasound (US) evaluation showed a hypoechoic 7.5-cm lesion in the pancreatic tail as well as several hypoechoic hepatic lesions. The findings were confirmed with multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) (Fig. 1A). US-guided biopsy specimen showed "cells compatible with well differentiated insulinoma" for the pancreatic lesion and "neuroendocrine tumour metastasis" for the hepatic lesions. Two sessions of radiotherapy were performed, along with medical treatment using diazoxide, but the patient had only minor improvement of quality of life. The hypoglycemic crises decreased

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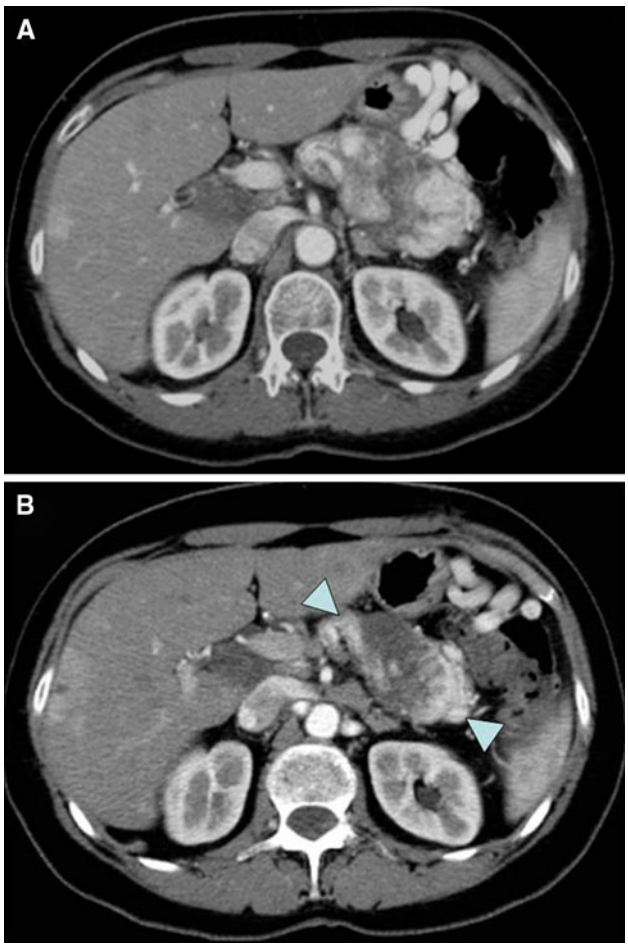

Fig. 1 Contrast-enhanced MDCT of patient no. 1 **A** before treatment and **B** 9 months after treatment. The lesion appeared diminished in dimensions, relatively hypodense, and had a smaller residual enhancing region (*arrowheads*)

in frequency, and the patient gained some weight. However, the number of hepatic metastases increased, and lung metastases also developed. The patient was retained nonoperable, but because her symptoms persisted, HIFU treatment was performed. The symptoms gradually disappeared in the first month after HIFU, whereas the lesion appeared widely hypodense with a minor residual enhancing region on control MDCT scans performed at 1, 3, 6, and 9 months (Fig. 1B). However, the hepatic and lung lesions remained unaltered. Despite the fact that the hepatic and lung lesions did not show any signs of regression, the patient has had had no hypoglycemic crisis during 10-month follow-up.

Case No. 2: Clinical History

A 43-year-old woman had a long medical history regarding clear cell renal carcinoma related to Von-Hippel-Lindau disease as well as pancreatic insulinoma located in the pancreatic body. The patient underwent left nephrectomy and partial pancreatectomy in 2000 for insulinoma. Three years later, renal tumour recurrence occurred, and treatment with RFA and radiotherapy was performed. Eight years after surgery, the pancreatic tumor recurred. Magnetic resonance imaging (MRI) showed a 2.4-cm lesion in the pancreatic body, and histology confirmed a well-differentiated insulinoma, which was causing nightly hypoglycemia (decreased glucose concentration of 35 mg/dl [1.94 mmol/dl]). The lesion was considered nonoperable because of local advancement and patient comorbidities. The lesion was not responsive to medical treatment with diazoxide; therefore, treatment with HIFU was decided. No complications occurred after treatment. The patient had pain relief, and MDCT 24 h later showed complete lack of lesion enhancement (Fig. 2A). The patient remains free of symptoms at 9-month follow-up, and there has been no enhancement on MDCT (Fig. 2B).

HIFU Treatment for Both Patients

Informed consent was obtained from both patients. Pretreatment planning was performed with US, and no gas interfered in the acoustic pathway. The skin overlying the lesion was carefully shaved to avoid any potential hair interference. General anesthesia was administered. A purified-water balloon was used to push and compress bowel loops to avoid unexpected presence of air in the beam pathway and to provide bowel-movement control (Fig. 3). After being anesthetized, the patient was carefully positioned in a prone position on the HIFU table, making sure that the skin overlying the target lesion was in contact with the degassed water. A vertical scanning mode was chosen, and there was a 5-mm distance between each slice. HIFU ablation was performed using the JC-HIFU system (Chongqing Haifu-HIFU-Tech, Chongqing, China). The therapeutic procedure was guided by real-time US. Therapeutic US energy was produced by a transducer with a diameter of 20 cm, a focal length of 15 cm, and a frequency of 0.8 MHz. A MyLab70 US imaging device (Esaote, Genova, Italy) was used as the real-time imaging unit. This 1.0- to 8.0-MHz imaging probe is located in the center of the HIFU transducer.

By scanning with the HIFU beam, the targeted region in each section was also ablated. This process was repeated on a section-by-section basis to achieve complete lesion ablation. During HIFU ablation, the real-time US scans obtained immediately before and after individual energy exposures were compared to determine changes in the ecogenicity of the treated region, which indicates the extent of coagulation necrosis. After several sonications, consistent ecogenicity change was observed in the lesions and

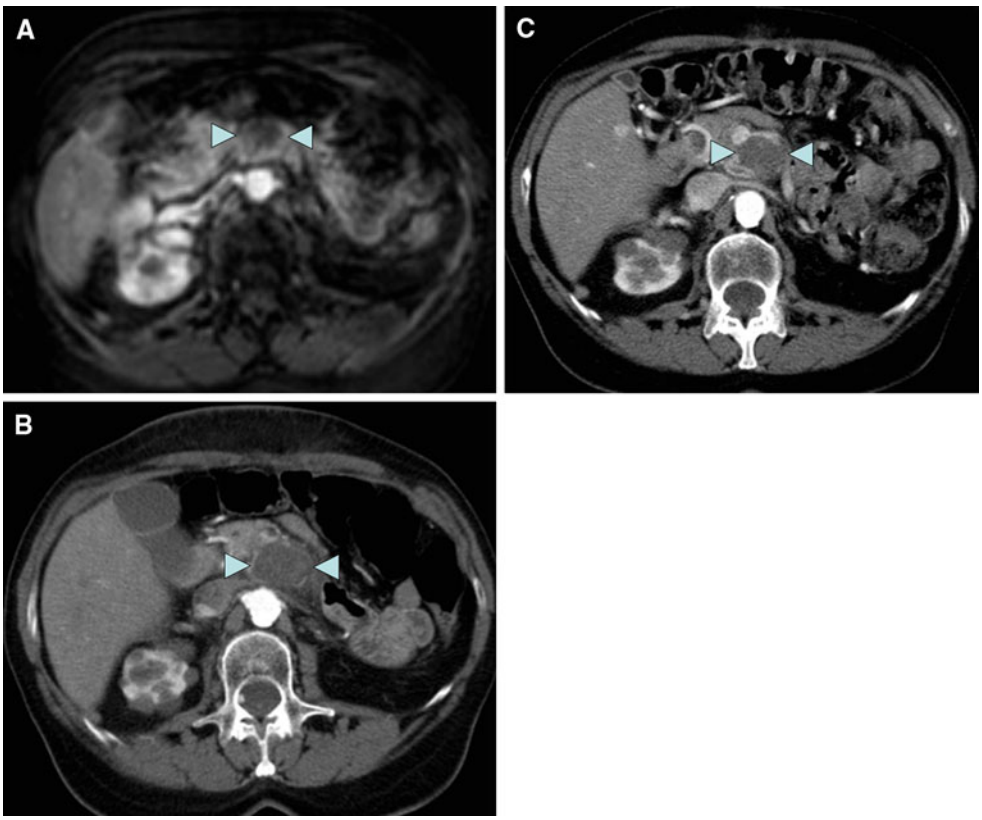

Fig. 2 Patient no. 2. **A** MRI after administration of contrast medium, performed before HIFU ablation, shows a 2.4-cm lesion of in the body of the pancreas that enhances peripherally (*arrowheads*). **B** MDCT performed 24 h after HIFU ablation shows ablation of entire lesion, as defined by the lesion's hypodensity and lack of enhancement, without complications (*arrowheads*). **C** MDCT scan 9 months after treatment shows that the lesion appears slightly diminished in dimensions but widely hypodense and without residual enhancing region (*arrowheads*)

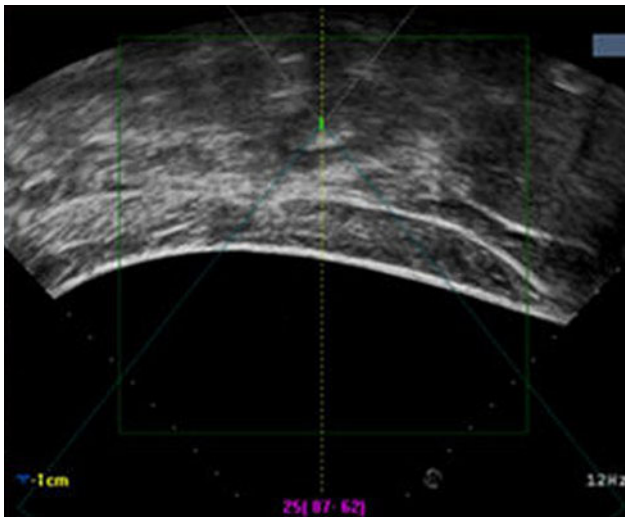

Fig. 3 Patient no. 1. After several sonications, consistent ecogenicity change was observed in the lesions, which was interpreted as satisfactory tissue ablation and also indicated the end of the procedure. Note the presence of the purified-water balloon that compresses bowel loops to avoid unpredicted presence of air in the beam pathway

interpreted as satisfactory tissue ablation and also indicated the end of the procedure (Fig. 3). Total time (preparation and treatment) was 4 h in the first case and 4 h and 25 min in the second case. Procedural time (time from the lesion localization to the last sonication) was 2 h in the first case and 2 h and 15 min in the second case. We also calculated total sonication time, defined as the exposure time, which is related to lesion size and blood supply; it was 1500 and 1560 s in the two cases, respectively. The treatment power used ranged between 360 and 410 W.

Results

Postprocedural MDCT at 24 h in the first case showed ablation of 70% of the lesion volume with presence of a residual enhancement rim. In the second case, control MDCT showed ablation of the entire lesion as defined by the lesion's hypodensity and lack of enhancement.

Results were considered satisfactory on the basis of formation of necrotic tissue in the lesions as well as patient

clinical signs and symptoms. After treatment, neither patient experienced any additional episodes of hypoglycemia. The day after treatment, blood glucose concentrations were slightly increased: 114–182 mg/dl (6.3–10 mmol/dl) in the first patient and 121–187 mg/dl (6.7–10.3 mmol/dl) in the second patient. No ablation-related complications occurred. Laboratory studies showed normal serum amylase levels (83 U/l for the first patient and 79 U/l for the second patient) 24 h after the procedure. No clinical signs of pancreatitis were detected, and both patients were discharged the day after procedure without any symptoms.

Follow-up MDCT performed at 1, 3, 6, and 9 months after HIFU showed lesion hypodensity, decreased size, and persistence of lack of enhancement, suggesting successful local tumor control.

Discussion

The therapy of choice for patients with pancreatic insulinomas is surgical enucleation or resection with curative intent. Surgery may be curative in 75% to 98% of patients [1]; however, it bares a considerable risk of morbidity and mortality. In case of inoperability, it is still unclear what should be the best alternative solution for patients with advanced pancreatic endocrine tumors [7].

Medical treatment, diazoxide in particular, decreases insulin secretion in the pancreatic islet cells. In the results of a study by Gill et al. [2], diazoxide was effective in 59% of the patients studied, with total suppression of hypoglycemia, and was partially effective in 38% who suffered from mild and occasional symptoms. Although we prescribed diazoxide in daily doses $\leq$300 mg, it did not control symptoms in either of our patients.

Local ablative therapies have an established role in tumour management. The efficacy and safety of tumor ablation with RFA is widely accepted for the treatment of solid tumours [8], but the technique is not yet standardized for pancreatic malignancies. Recently, Limmera et al. reported RFA as a clinically successful technique for pancreatic insulinoma in a nonoperable patient [3]. Furthermore, published data suggest that RFA can be used to control symptoms of liver metastases of patients with neuroendocrine tumors [9]. Nevertheless, RFA is not without complications, particularly in an anatomically challenging location, such as the pancreas. Elias et al. [10] used RFA to treat two patients with pancreatic metastases of renal cell carcinomas. In the first patient, a pancreatico-cutaneous fistula developed that necessitated laparotomy. In the second patient, severe necrotizing pancreatitis developed. Matsui et al. [11] used RFA for selective thermocoagulation of unresectable pancreatic carcinomas and reported two deaths from severe complications in 20 treated patients.

Other local ablative techniques, such as microwave ablation, cryoablation, and photodynamic therapy, have been described and may have role in the ablation of pancreatic tumors in the future [12]. However, the delicate nature of the pancreatic parenchyma, the predisposition to pancreatitis, and the risk of injury of important adjacent structures, such as the duodenum or the common bile duct, have been the main limiting factors in the application of these ablative techniques to the pancreas.

Percutaneous embolization of insulinomas has been described as a treatment for nonsuitable surgical candidates in just a few cases in the literature [4, 5]. Embolization, although promising, is still based on empiric knowledge and is also invasive; therefore, complications such as pancreatitis are rather difficult to avoid [5].

As a less-invasive technique, HIFU is receiving increasing interest for the treatment of several primary tumors and metastasis [13]. Wu et al. reported achieving large areas of coagulation necrosis with this technique when treating patients with hepatocellular carcinoma [14]. Zhang et al. reported that HIFU may achieve complete tumor necrosis even when the lesion is located adjacent to major hepatic blood vessels [15].

In another study. Wu et al. described that HIFU is safe and feasible for the treatment of patients with pancreatic cancer. No skin burns occurred, and there was no evidence of postprocedural pancreatitis, peritonitis, or jaundice in any patient during the follow-up period [6].

In the cases described here, needle insertion would have been rather challenging without being able to exclude the potential risk of thermal injury of anatomic structures adjacent to the lesion. Because the recurring episodes of severe hypoglycemia strongly impaired our patients, we decided to attempt HIFU as a less-invasive treatment method.

HIFU achieves ablation by way of focused US energy from an external source that is targeted within the body, resulting in thermally induced necrosis. Acoustic energy is absorbed, and heat is generated by delivering high-acoustic intensity to the tissue. Because it is focused, the acoustic intensity is high only within the focal region; however, outside the focal region, the intensity is substantially lower, thus minimizing the risk of unintended injury to the surrounding structures. HIFU can be used to reach tumors that are in unfavorable locations for needle placement, such in the cases described here, provided there is an acoustic window to allow the transmission of US energy.

In our patients, HIFU proved to be a clinically successful procedure that offered better disease control and quality of life. Patients became free of symptoms, and no complications occurred.

The limitations of the method are the fact that in most cases, general anesthesia is required; that the ablation may

not be radical; and that we still do not know the long-term results after HIFU.

Nevertheless, we believe HIFU appears to be a valid alternative therapeutic strategy that may easily be repeated, thus providing good local tumor control in patients with inoperable and symptomatic pancreatic neuroendocrine tumours (NETs) and no indication for an alternate minimally invasive approach. In addition, this method could be considered as a cytoreductive measure in an adjuvant setting with the aim of better palliation in patients with locally advanced pancreatic malignancies; however, further studies with or without chemotherapy and radiotherapy are warranted to evaluate the benefit of HIFU regarding patient survival and quality of life.

Until direct comparison with the established therapeutic strategy of NETS is performed, HIFU should be reserved for the treatment of patients whose symptoms cannot be controlled by medical therapy and who are not candidates for surgery or any other minimally invasive treatment.

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