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Case report

Unresectable giant pancreatic neuroendocrine tumor effectively treated by high-intensity focused ultrasound: A case report and review of the literature

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ABSTRACT

Patients with pancreatic neuroendocrine tumors (PNETs) diagnosed at late stage are not suitable candidates for surgery. So far, only a limited number of cases have been documented in literature about the effectiveness of HIFU, which has been more frequently reported to treat pancreatic adenocarcinoma rather than PNET. We report herein that a patient with a pancreatic neuroendocrine unresectable tumor was effectively treated with serial high-intensity focused ultrasound (HIFU) ablation, with no significant side effects detected. Upon evaluation, treatment results included: the tendency of tumor shrinkage, pain relief, decreased tumor marker levels, and obvious improvements in quality of life. Sustained efficacy was observed during a follow-up at 25 months with no tumor progression.

1. Case report

An 80-yr-old male patient complaining of persistent upper quadrant abdominal pain, dyspepsia, and insomnia due to pain for 5 days was admitted to the Shanghai Cancer Center in Shanghai, China, in June, 2011. Upon careful physical examination, a mass in his upper abdomen was found to be hard, unmovable, and painful on palpation. CT scan revealed a massive lesion (10.1 cm * 9.4 cm) in the body and tail of the pancreas with local lymphatic metastases surrounding the spleen artery. The patient then received laparotomy and widespread peritoneal dissemination was detected in the surgery, which avoided a radical resection. A biopsy of the metastatic nodule of the greater omentum was performed. The postoperative pathologic study revealed the nodule with metastatic NET. Five mitotic figures were present in 16 high-power fields. Immunohistochemical stains showed CK7(+), CK8(−/+), SYN(+), CHG(+), and 15% of tumor cells were positive for Ki67 (Fig. 1).

After recovery from the surgery, the patient was instructed to rate his level of pain in the morning upon awakening using the numeric rating scale (NRS) of pain intensity. He rated his pain intensity “8 out of 10” on a scale of 0 (no pain) to 10 (worst possible pain). The patient did not have flushing of face, palpitation, diarrhea, jaundice, peripheral edema, or any other significant symptom. Blood tests showed an elevated serum chromogranin A (CgA: 214 ng/ml; range: 0–100 ng/ml) and neuron specific enolase (NSE: 62.9 μg/L; range: 0–16.3 μg/L). CA19-9, AFP, CEA, CA50, CA242, CA724 were within normal level. Serum gastrin, vasoactive intestinal peptide, C-peptide, glucagon, calcium, and parathormone were also tested with no positive findings detected, suggesting that the tumor was functionally inactive. His Karnofsky performance status score of 70. Routine blood test revealed white blood cell count of 2.2×10^9/L and a neutrophil count of 1.1×10^9/L; platelet and hemoglobin levels were normal. The patient’s past medical history was not significant, except for leucopenia of unknown origin for 8 years.

Finally, the patient was diagnosed with functionally inactive PNET; classified as Grade 2 and Stage III (T3N1M0), according to the WHO 2010 and AJCC systems of nomenclature for neuroendocrine tumors, respectively.

Aiming to achieve an analgesic effect and local control of the lesion simultaneously, HIFU was determined to be the treatment option for the patient. HIFU treatments were performed in July, October, and December, 2011. Before the procedure, informed consent was obtained from the patient. To ensure a safe acoustic

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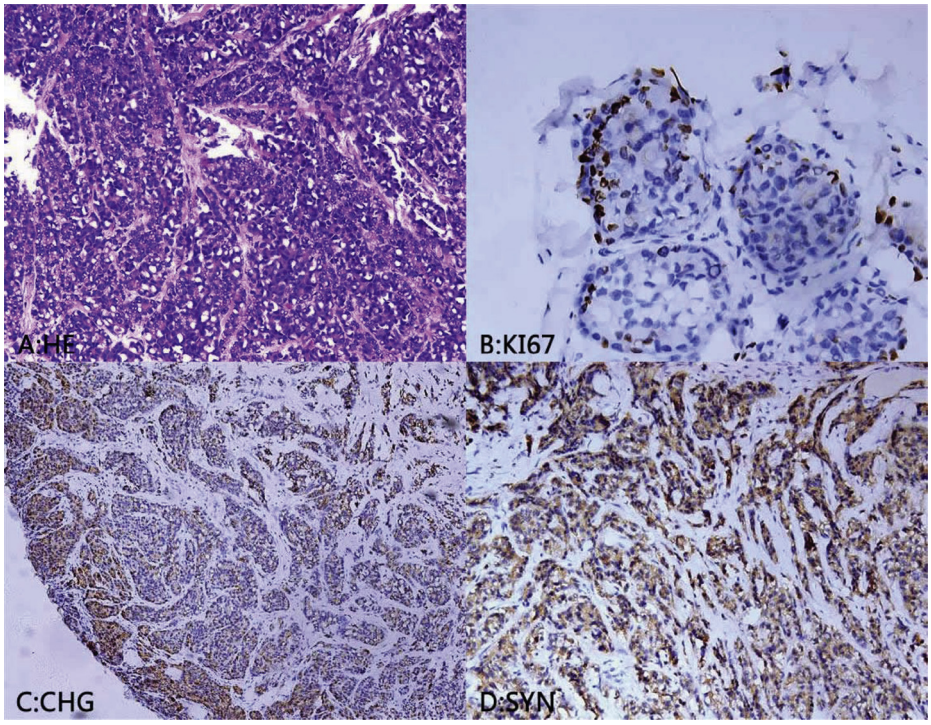

Fig. 1. The pathological finding of the metastatic nodule of greater omentum. A. H&E stain: the tumor cells showed an organoid/nested growth pattern. B. Immunostaining revealed 15% of tumor cells positive for Ki-67. C. Strong staining for chromogranin. D. Strong staining for synaptophysin.

pathway, preoperative fasting and catharsis were performed to evacuate gas and food residues in the gastrointestinal tract. Skin at the tumor region was carefully shaved, defatted and degassed. After proper sedation and anesthesia with midazolam and morphine, the patient was positioned prone on the HIFU table, and the skin overlying the target lesion was placed in contact with degassed water. The procedure was completed under the guidance of real-time ultrasound using the JC-HIFU system (Chongqing Haifu-HIFU-Tech, Chongqing, China). With a 5-mm distance between slices, each slice of the targeted lesion was carefully and completely ablated from the deepest to the shallowest parts of the tumor, with a focal length of 135 mm and frequency of 0.85 MHz. The total energy was 234 W, 243 W and 265 W, with treatment time 1026 s, 940 s, and 952 s, respectively. The ultrasound images before and after each HIFU treatment are shown in Fig. 2.

During and after HIFU, the patient was monitored with electrocardiogram, without abnormalities present. There was no evidence of significant complication or acute pancreatitis upon biochemical analysis either. After 3 cycles of HIFU, the patient was determined to be treatment-free.

Encouragingly, after three cycles of HIFU treatment, he experienced significantly reduced abdominal pain, rating the pain a "1 out of 10" on the NRS of pain intensity. During the 25 month follow-up, the patient's abdominal pain had almost completely been eliminated. CT scan revealed that the ablated lesion in the pancreas was stable (Fig. 3) and had a tendency to shrink in volume. Further, serum CgA and NSE levels gradually returned to normal (35.1 U/L and 11.2 μg/L) and remained stable. Appetite and sleep were also remarkably improved. Currently, the patient is alive and in good condition without distant metastasis or abdominal pain, except for occasional discomfort when consuming too much food. A follow-up at 25 months showed neither tumor progression nor distant metastasis. According to the WHO Criteria for Response, the patient was classified as having stable disease.

2. Discussion

Pancreatic neuroendocrine tumors (PNETs), which represent approximately 2% of all pancreatic neoplasms, are a relatively rare subgroup of tumors found in the pancreas [1,2]. Thus far, surgery has been the only curative treatment for patients with removable PNET, with a reported 5-yr survival rate of 80% for nonfunctioning PNET cases [3]. Unfortunately, patients diagnosed at advanced stage or with poor physical status may not be prospective candidates for surgery, and will almost always suffer from chronic abdominal pain. Considering the patient's overall presentation, including the status of the lesion, relatively older age, a less-than-normal performance status, and leukopenia, a highly traumatic radical surgery was considered risky.

Therefore, an appropriate treatment modality, tailored specifically to him, neither too conservative nor too aggressive may be a good option.

Currently, because of the heterogeneity of PNET, there is no accepted standard management for patients with unresectable PNET. Furthermore, there are no standard adjuvant or neo-adjuvant therapies for PNETs. Streptozotocin-based chemotherapy may modestly benefit some patients with advanced PNET, but may not be very effective at relieving pain [4]. Additionally, in the case of the current patient, active chemotherapy could aggravate his leucopenia, inducing neutropenia and a serious life-threatening infection. While everolimus [5], long-acting octreotide [6], and sunitinib [7] have all been proven effective in clinical trials in advanced stage PNETs and may be suitable options for the current patient, but the high cost of these medications in China may be a financial burden to patients and preclude their use. Painkillers are the most commonly-used medications to alleviate pain, but it is simply a measure of expediency. Neurolytic celiac plexus block (NCPB) is another method for the treatment of pancreatic cancer pain. Nevertheless, because of the risks associated with NCPB, the patient