

Diagnosis and comprehensive treatment of a glucagonoma in a patient with residual intrahepatic metastases postoperatively: A case report and literature review

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Abstract. Glucagonomas are rare neuroendocrine neoplasms of the pancreas with malignant potential. At present, their epidemiology is not entirely clear, so clinicians are not well versed, lacking any consensus on diagnosis or comprehensive treatment. The present study reports the case of a 32-year-old woman hospitalized for recurrent glossitis, perioral dermatitis and necrolytic migratory erythema (NME) of both lower limbs. Imaging studies revealed a low-density nodule (~2 cm) in the tail of the pancreas, as well as multiple space-occupying hepatic lesions. Surgical intervention was then selected, and distal pancreatectomy, splenectomy and palliative metastasectomies were performed. Tissue examination subsequently confirmed a primary pancreatic neuroendocrine tumor (grade 2), metastatic to the liver. The NME resolved postoperatively, aided by intramuscular injections of long-acting release octreotide (30 mg) every 28 days. A series of three percutaneous ablative treatments (microwave ablation) were also undertaken within a 2-year period, targeting the liver metastases. The present condition of the patient is good, with no cutaneous relapse to date. Palliative metastasectomies, in conjunction with ablative treatments and combination somatostatin analog (SSA) use, are unique aspects of this case that, to the best of our knowledge, have yet to be documented in the literature. Surgical palliation may benefit patients with liver involvement and prolong their survival time. Likewise, ablative treatments and SSA injections delivered together not only address hepatic spread, but also control hormone-related symptoms, having a positive impact

on prognosis. As glucagonomas are so rare, there is no real agreement on their management. The present study aims to guide clinical practice by adding further to the available data.

Introduction

Glucagonoma is a rare neuroendocrine tumor (NET) that arises from α -islet cells, representing 1% of all pancreatic NETs; its annual incidence worldwide is only ~1 per 20 million (1,2). Overproduction of glucagon, with necrolytic migratory erythema (NME), is the hallmark of glucagonoma and typically the first observed symptom. Other clinical findings include diabetes mellitus, anemia, weight loss, fat leakage and diarrhea (2,3). The clinical course may also be complicated by venous thrombosis, pulmonary embolism (30-50%) and various neuropsychiatric disorders, namely depression, psychosis, agitation, dementia, paranoid delusions, ataxia, hyperreflexia and optic atrophy (4,5). Despite a benign nature for some, the rate of malignant transformation is substantial (50-80%), with metastases generally present at the time of diagnosis (3,6). The liver and lymph nodes are the usual sites of spread (6).

Early and accurate diagnosis of glucagonoma may ensure proper management and improve the prognosis. Currently, surgical resection is the chief consideration (3), whereas the treatment of metastasis remains controversial. Thus far, available options [i.e., medical management, palliative surgery, chemotherapy, somatostatin analog (SSA) use and others] have yielded poor results in terms of overall survival and prognosis (7,8). A comprehensive and surgically oriented approach is perhaps the best means of optimizing long-term prognosis in instances of metastatic glucagonoma (9).

The present study reports the case of a 32-year-old female patient with glucagonoma, marked by multiple intrahepatic metastases and pathognomonic NME. The diagnostic and therapeutic challenges of managing initially advanced disease and later postoperative recurrences are also discussed.

Case report

Patient case. A 32-year-old female patient was hospitalized at the First Hospital of China Medical University (Shenyang, China) in September 2021, primarily for perioral dermatitis

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Table I. Clinical data and laboratory testing.

Parameter	Value	Reference range
Clinical data		
Age, years	32	-
Weight, kg	45	-
BMI	17.58	-
Blood pressure, mmHg	125/82	-
Heart rate	111	-
Respiratory rate	17	-
Temperature	36.5	-
Laboratory data		
K ⁺ , mmol/l	3.50	3.50-5.30
Cl ⁻ , mmol/l	112.0	98.0-107.0
RBC, x10 ¹² /l	3.60	3.80-5.10
Hb, g/l	99	115-150
CRP, mg/l	71.00	0.00-6.00
GLU, mmol/l	3.80	3.90-6.10
HbA1C, %	5.4	3.9-6.1
AST, U/l	24	13-35
ALT, U/l	34	7-40
GGT, U/l	54	7-45
CA19-9, U/l	6.29	40.00-530.00
CA72-4, U/l	2.98	0.77-33.03
NSE, ng/ml	16.36	0.00-16.00
ACTH, pg/ml	8.87	7.20-63.30
COR, nmol/l	471.00	171.00-536.00
LH, mIU/l	5.51	1.10-11.60
FSH, mIU/l	10.60	2.80-11.30
PRG, pmol/l	<0.64	0.64-3.60
PRL, mIU/l	562.00	40.00-530.00
E2, pmol/l	<73.40	91.75-275.25

BMI, body mass index; RBC, red blood cell; Hb, hemoglobin; CRP, C-reactive protein; GLU, glucose; HbA1C, haemoglobin A1C; AST, aspartate transaminase; ALT, alanine transaminase; GGT, γ -glutamyl transferase; CA19-9, cancer antigen 19-9; CA72-4, cancer antigen 72-4; NSE, enolase; ACTH, adrenocorticotropic hormone; COR, cortisol; LH, luteinising hormone; FSH, follicle-stimulating hormone; PRG, progesterone; PRL, prolactin; E2, estradiol 2.

(Fig. 1A) and lower-limb NME (Fig. 1B) for a 2-month duration. Glossitis was also problematic for nearly 6 months. The patient had no family history of endocrine diseases, particularly diabetes. Laboratory testing indicated the following: i) mild anemia (Table I); ii) increases in neuron-specific enolase (NSE) and C-reactive protein (CRP) (Table I); and iii) oral glucose tolerance test (OGTT) abnormality (Table II). These findings signaled insulin resistance, despite a marginally low fasting blood glucose level. Plasma glucagon analysis indicated >10 times the upper limit of the normal range (124.00 pmol/l) (Fig. 2), and serum prolactin was elevated, but there was no imaging evidence of adenomas (parathyroid or pituitary) or other related pathology (Table I). On enhanced abdominal computed tomography (CT), a low-density defect



Figure 1. Evolving cutaneous manifestations. Initial presentation: (A) Perioral dermatitis and (B) lower-limb NME. After surgery: (C) Perioral dermatitis and (D) lower-limb NME. Postoperative month 7 (completely resolved): (E) Perioral dermatitis and (F) lower-limb NME.

of the pancreatic tail (~1.9x1.6 cm) and multiple low-density hepatic lesions (Fig. 3A and B) were visible. Positron emission tomography-CT confirmed increased metabolic activity at both pancreatic (Fig. 3C) [maximum standardized uptake value (SUV_{max}), 3.6] and intrahepatic sites (Fig. 3D-F) SUV_{max}, 4.5), while excluding involvement elsewhere. The aforementioned features were interpreted as a glucagonoma, with multiple intrahepatic metastases.

Hepatic spread ordinarily would preclude a complete resection. However, the patient's liver was functionally intact (Table I), the patient was young and in otherwise good health, and no invasion of the main artery was evident. Consequently, a distal pancreatectomy and splenectomy (DPS), with palliative resections of the hepatic metastases, was performed. Tissue examination thereafter confirmed a primary pancreatic neuroendocrine tumor [grade 2 (1)] (Fig. 4A-E), metastatic to the liver (Fig. 4F-J). Both primary and metastatic lesions proved immunohistochemically positive for glucagon [pancreas, 40%+ (Fig. 4D); liver, 90%+ (Fig. 4I)], synaptophysin (Syn) (Fig. 4B and F) and chromogranin A (CgA) (Fig. 4C and H). The Ki-67 indices were 15% each (Fig. 4E and J).

After surgery, the patient was administered periodic intramuscular injections (every 28 days) of a long-acting release (LAR) octreotide (30 mg) formulation as long-term therapy (a total of 18 times to date). The erythema of both lower limbs (Fig. 1C and D) resolved by postoperative day 7, as did the oral manifestations. The serum glucagon level also normalized

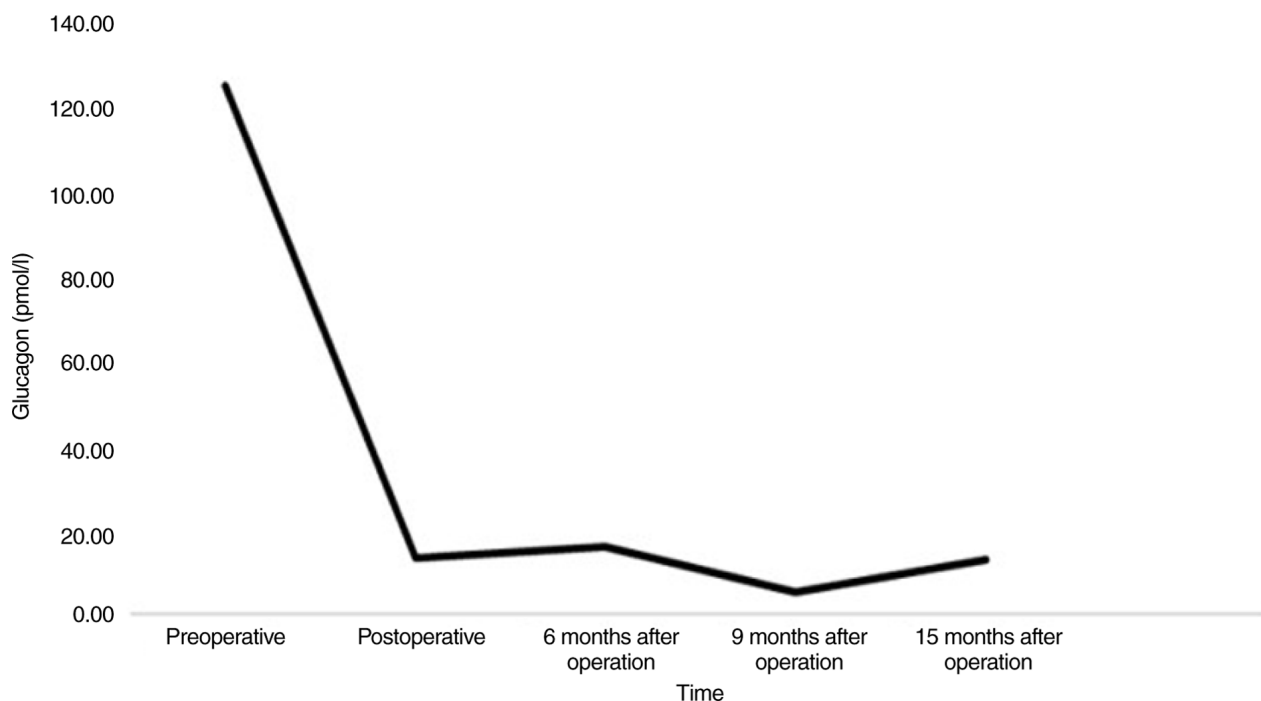


Figure 2. Timeline of serum glucagon decline and normalization.

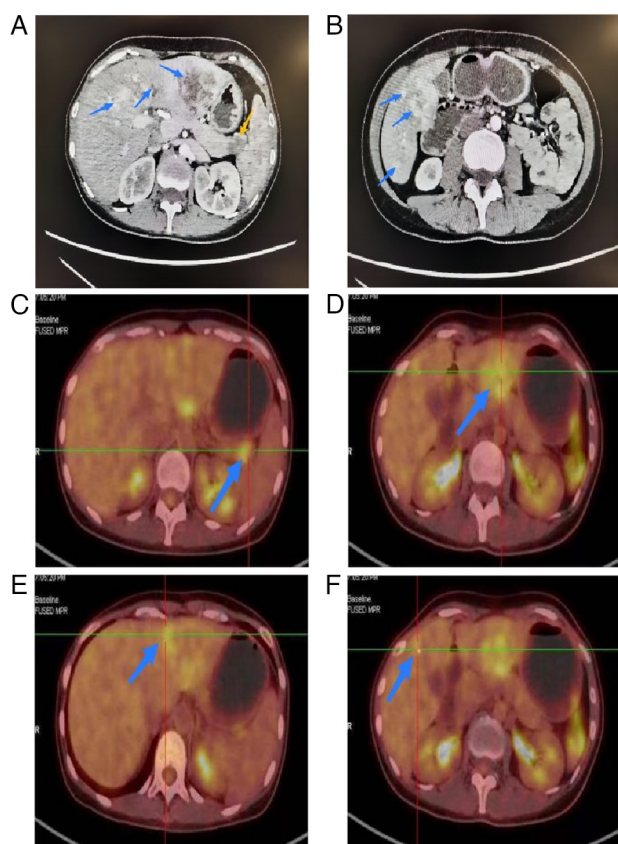


Figure 3. Abdominal imaging studies prior to surgery. (A and B) Enhanced CT showing a mixed-density nodule (1.9x1.6 cm) at the tail of the pancreas and multiple hepatic lesions (yellow arrows indicate pancreatic lesions; blue arrows indicate liver metastases). (C-F) Positron emission tomography-CT images of (C) the same pancreatic nodule displaying increased metabolism (SUV_{max} , 3.6) and (D-F) multiple, somewhat low-density lesions of the liver (SUV_{max} , 4.5) with uneven metabolic activity (malignancy not excluded) (blue arrows indicate liver metastases). CT, computed tomography; SUV_{max} , maximum standardized uptake value.

(13.34 pmol/l) (Fig. 2), in sharp contrast with the preoperative baseline. However, multiple low-density hepatic lesions reappeared on the 6-month follow-up CT scans. Initially, CT-guided microwave ablation (tumor in right anterior lobe of liver: 50 W for 8 min; tumor in right posterior lobe of liver: 60 W for 10 min) was performed, with post-treatment CT imaging (Before: Fig. 5A-C; after: Fig. 5D-F). CT imaging at the patient review performed at 10 months postoperatively showed that the liver lesions were smaller than before (Fig. 6A and B). CT-guided microwave ablation (tumor in right anterior lobe of liver: 70 W for 5 min; tumor in right posterior lobe of liver: 60 W for 8 min; tumor in left medial lobe: 60 W for 5 min) was also undertaken at 18 months postoperatively (before: Fig. 7A-C; after: Fig. 7D-F) and ablation (lower end of right lobe, top end of diaphragm and right anterior lobe of liver: 60 W for 8 min each) was performed at 24 months postoperatively (before: Fig. 8A-C; after: Fig. 8D-F), targeting all tumor recurrences. A percutaneous needle biopsy obtained prior to ablation disclosed tumor angiogenesis; but the residual neuroendocrine tumor (grade 2) was no longer positive for glucagon (Fig. 9), and serum glucagon levels had stabilized, falling within the normal range (5.35 pmol/l) (Fig. 2). To date, intramuscular administration of LAR octreotide has continued every 28 days at the same dose, without complications or adverse reactions. The patient was treated every 28 days and followed up at the same time. The last visit was in mid-January 2024. There was no evidence of local or systemic recurrence.

Pathology

Hematoxylin and eosin staining. Tissues was fixed with 10% neutral formalin at room temperature for 16-18 h, and then cut into 4- μ m thickness. The sections were dewaxed at 45°C for ~5 min. The sections were stained with hematoxylin and eosin

Table II. Oral glucose tolerance test.

Parameter	Normal range	0 min	30 min	60 min	120 min	180 min
Glucose, mmol/l	3.90-6.10	3.97	11.70	14.42	15.00	7.27
C-peptide, pmol/l	99.90-1242.00	836.40	2,978.30	5,554.80	7,652.60	6,562.20
Serum insulin, mIU/l	4.03-23.46	11.65	75.26	158.60	297.30	186.70

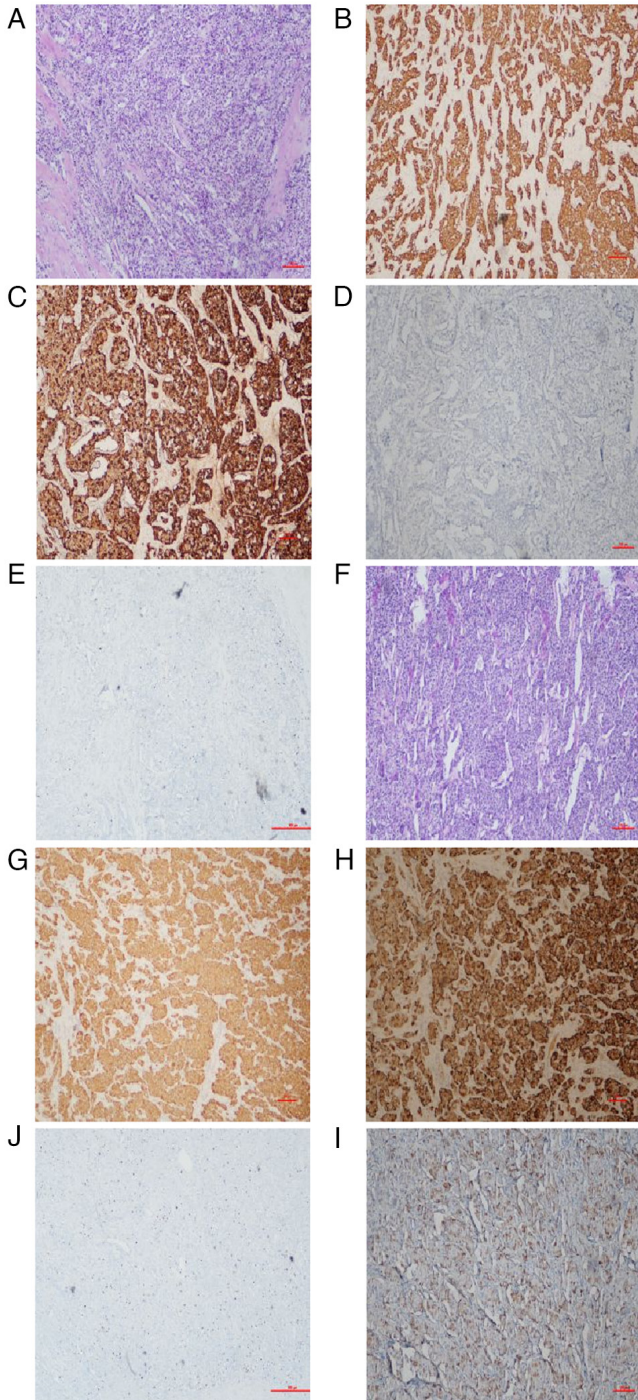


Figure 4. Histological sections of the tumor. (A-E) Staining in the pancreas, including (A) routine H&E stain (x100 magnification) and (B-D) positive immunostaining for profile Syn, CgA and glucagon (40%+), with (E) a Ki-67 index of 15% (x100 magnification). (F-J) Staining in the liver, including (F) routine H&E staining (x100 magnification) and (G-I) positive immunostaining for Syn, CgA and glucagon (90%+), with (J) a Ki-67 index of 15% (x100 magnification). H&E, hematoxylin and eosin; Syn, synaptophysin; cCgA, chromogranin A.

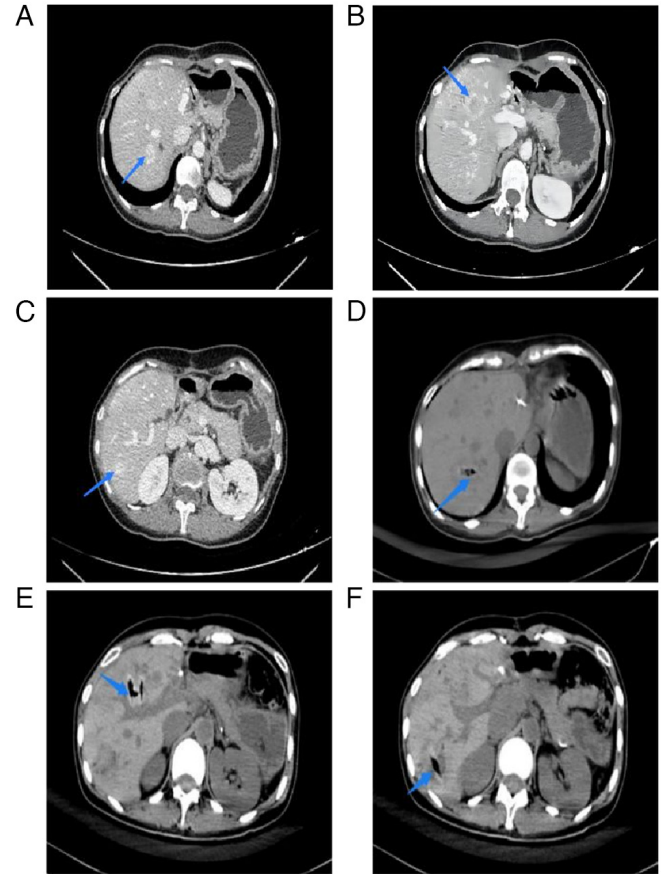


Figure 5. CT (enhanced) acquired at postoperative month 6. CT images (A-C) before and (D-F) after radiofrequency ablation of residual liver metastases. CT, computed tomography (the arrow indicates the liver metastasis lesion location).

at room temperature for 3.75 min using the Roche Ventana HE 600 automatic staining system (Roche Diagnostics), and then sealed with neutral gum. The staining was evaluated under a light microscope at x100 magnification.

Immunohistochemical staining. The sections were dewaxed at 45°C for ~5 min, and then repaired with immunohistochemical antigen repair solution (neutral) at 99°C for 20 min. The antibodies (immediate-use Syn antibody reagent; cat. no. 20180177; immediate-use CgA antibody reagent; cat. no. 20180186; immediate-use glucagon antibody reagent; cat. no. 20180317; immediate-use Ki-67 antibody reagent; cat. no. 20180160) (all Fuzhou Maixin Biotech Co., Ltd.) were separately added to the BenchMark XT on the Roche Ventana platform at 32°C for 30 min. After washing with PBS, DAB staining was performed at 36°C using 25 ml ultraView Universal DAB Inhibitor (3% H₂O₂) for 8 min, 25 ml ultraView Universal HRP Multimer (55 μg/ml) for

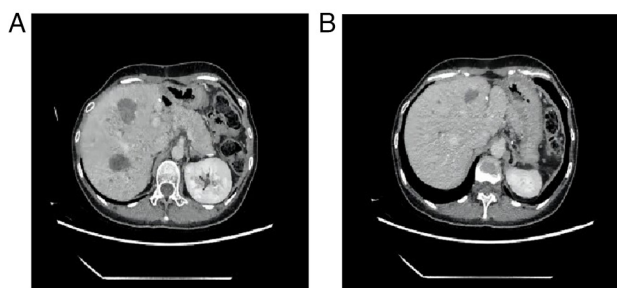


Figure 6. CT (enhanced) acquired at postoperative month 10. (A and B) CT images of multiple liver lesions after treatment. CT, computed tomography.

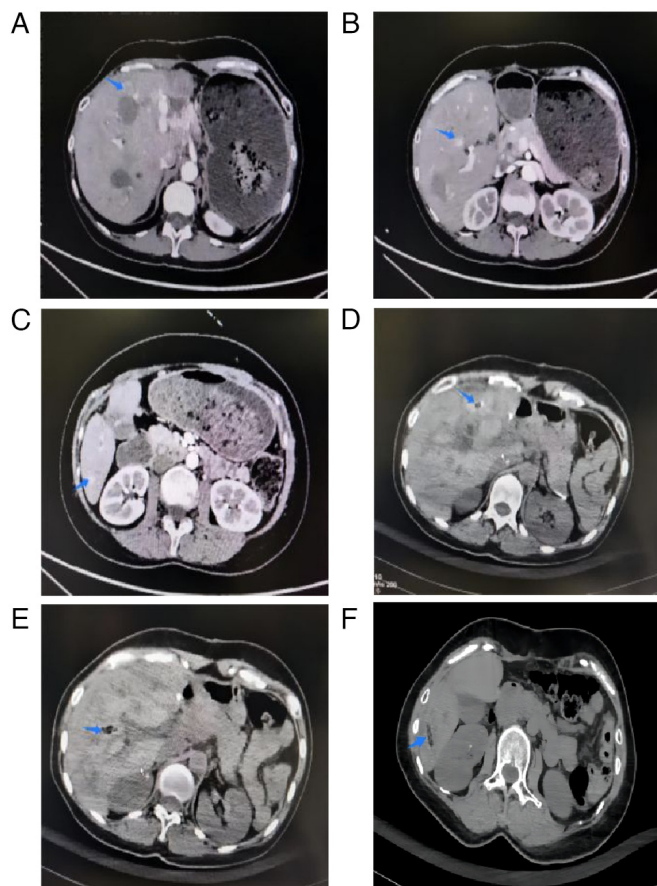


Figure 7. CT acquired at postoperative month 18. CT images (A-C) before and (D-F) after microwave ablation of residual liver metastases. CT, computed tomography (arrows indicate the liver metastasis lesion location).

8 min, 25 ml ultraView Universal DAB Chromogen (0.2% w/v DAB) plus 25 ml ultraView Universal DAB H₂O₂ (0.04% H₂O₂) for a total of 8 min, and 25 ml ultraView Universal DAB Copper (5 g/l CuSO₄) for 4 min. Washing with PBS was performed between each step. The sections were then mounted. Evaluation of staining was performed under a light microscope at x100 magnification.

Discussion

Glucagonomas are particularly rare neuroendocrine neoplasms (5,10). The neoplasms manifest clinically as glucagonoma syndrome, the hallmark of which is NME (10,11).

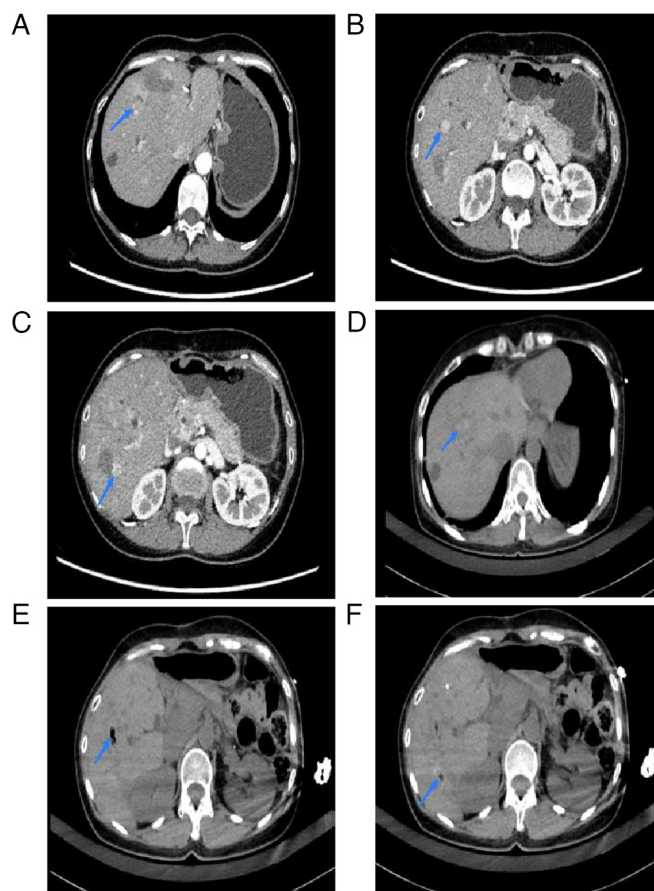


Figure 8. CT acquired at postoperative month 24. CT images (A-C) before and (D-F) after microwave ablation of residual liver metastases. CT, computed tomography (arrow indicates the liver metastasis lesion location).

Most of those previously reported had spread to the liver or lymph nodes and were overtly malignant, underscoring the importance of prompt detection (12,13). The patient treated in the present study was hospitalized primarily for NME, so it is apparent that clinical factors figure prominently in diagnostic accuracy (10,14). However, such determinations are not without difficulties. Most patients are diagnosed with diabetes or skin disease and the real lesion is missed (15,16). In our experience, a combination of clinical and laboratory findings works best, applying present-day diagnostic criteria for glucagonoma as follows: i) Elevated serum glucagon level by radioimmunoassay; ii) radiographic or histological evidence of a neuroendocrine tumor; and iii) characteristic clinical features (NME) (10,13,17). The relapse of NME is therefore a pivotal and telling development. In addition, the patients with pancreatic glucagonomas sometimes exhibit complications of pituitary and parathyroid tumors (13,15,16). In the present case, although the enhanced abdominal CT scan of the patient showed the pancreatic glucagonoma to be hypervascular, the case was not complicated by pituitary and parathyroid tumors.

Although benign on occasion, glucagonomas are often malignant and possibly have already disseminated at the time of discovery. The long-term prognosis is subsequently poor, despite an array of available therapeutic options (7,8). Conventional or laparoscopic resection is safe and effective, associated with low rates of recurrence; however, only

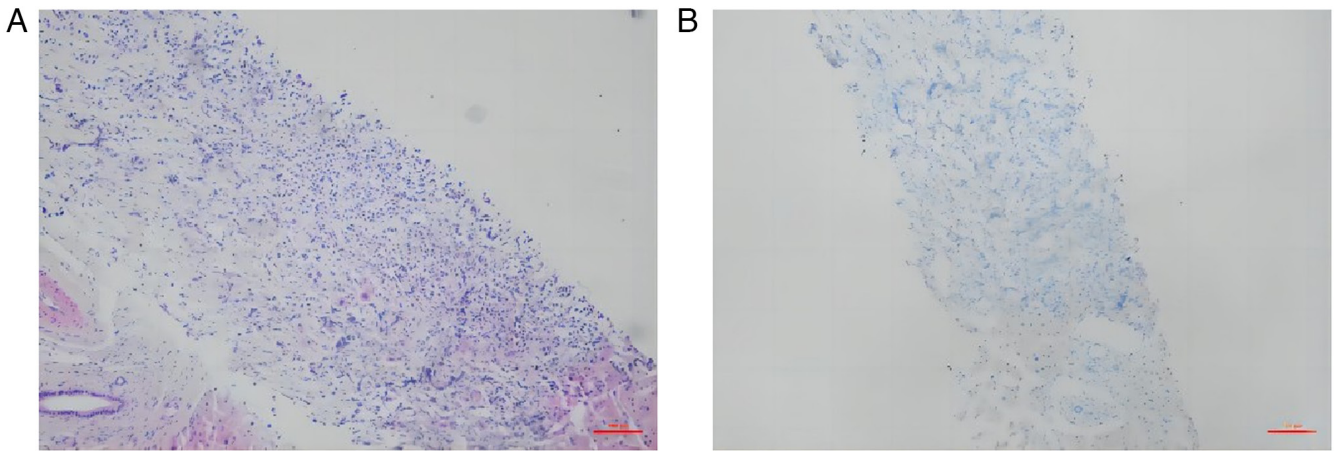


Figure 9. Histological sections of the residual neuroendocrine tumor. (A) Routine hematoxylin and eosin staining (x100 magnification) and (B) negative immunostaining for glucagon (scale bar, 100 μ m).

10-20% of patients are surgically curable, given the propensity for multicentric tumor dissemination (18). Ultimately, the benefits of surgery must be weighed against potential complications and mortality risks (19-21). In instances of liver metastasis, a surgical solution remains controversial, given the protracted and unpredictable course of glucagonomas. For the most part, surgical resection is still the mainstay of treatment for localized disease, whereas palliative cytoreductive surgery may help relieve symptoms and effectively confer prognostic improvement. Even with known metastasis, resecting the primary tumor prolongs patient survival (21,22).

Hormonal secretion by functional glucagonomas is most often suppressed through SSA use. These first-line agents for symptom control also exert certain anti-proliferative tumor effects, thus prolonging disease-free survival in some patients (23,24). While undergoing systemic treatment, patients with liver metastases <5 cm maximally (preferably <3 cm) may qualify for ablative treatments as well (25,26). Ablative interventions seem to boost symptom relief in this setting (lasting 14-27 months) and have generated 5-year survival rates of 57-80% (27).

The present patient harbored multiple metastases upon presentation. However, a younger age and favorable preoperative status permitted a DPS procedure, with palliative resections of existing hepatic nodules. Afterwards, the patchy changes to the facial and lower-leg skin gradually resolved. Serum glucagon levels were also monitored at intervals and marked improvement was found postoperatively. After 6 months, several hepatic lesions were again discovered, and the larger growths were subjected to percutaneous ablation. For the treatment of postoperative liver metastases in this patient, ablation therapy was more desirable than transarterial therapy (25,27). The patient continued to receive intramuscular injections of LAR octreotide (30 mg) while undergoing three separate ablative procedures. All existing hepatic disease was successfully eradicated as a result. Nonetheless, continued monitoring of serum glucagon and imaging parameters is obligatory.

To date, the patient's symptoms are gone, and the postoperative glucagon levels have normalized, aligning with the results of repeat immunostaining of glucagon expression in

a liver biopsy specimen. This indicates that the patient with multiple intrahepatic metastases may benefit from palliative surgery, conducting postoperative ablative treatments as needed during SSA administration. The prognosis corresponds well with tumor classification, grading and disease stage. The 5-year overall survival rate is ~54%, and the 5-year relative survival rates of localized, locally advanced and metastatic glucagonoma are 93, 77 and 27%, respectively (27,28). Although the expected survival time in instances of metastatic glucagonoma is ~20 months (28), the clinical course of the present patient indicates that prolongation is feasible, given a prompt diagnosis and optimal therapeutic choices.

In the event of multiple liver metastases, palliative metastasectomies and postoperative ablations may be beneficial and help prolong survival time, while achieving hormone-related symptoms control through SSA use (29-32). In the present study, the LAR formulation of octreotide was found to be an important and effective long-term therapy, although its merit may be debated due to the scarcity of data.

In conclusion, in patients with glucagonomas, the comprehensive treatment of advanced disease is a complex process, guided by overall patient fitness and tumor characteristics. A multimodal effort would be ideal, gathering as many patients as possible for analysis and exploring the full scope of individualized therapy. Managing these neoplastic oddities may then become more systematic and uniform to optimize patient outcomes.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

SY and MG communicated with various departments, collected patient information, and carried out clinical management and prognostic follow-up. CZ was responsible for obtaining medical images and analyzing data related to patient laboratory tests and imaging findings. LC provided and analyzed disease-related diagnostic and treatment information. LZ was responsible for the treatment of the patient, the preoperative clinical management, the formulation of treatment plans, the completion of the operation with Professor Chunlin Ge, and the comprehensive treatment in the perioperative period. SY and LZ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The patient provided written informed consent to participate.

Patient consent for publication

The patient provided written informed consent for publication of this report and the attached images.

Competing interests

The authors declare that they have no competing interests.

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