Glucagonoma and Glucagonoma Syndrome

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Glucagonoma : Neuroendocrine tumours of the pancreas (pNET)[1]

- Originate from alpha islet cells
- Synthesize and secrete glucagon or other peptides derived from preproglucagon gene
- Associated with a well described glucagonoma syndrome characterized by hyperglucagonemia, skin rash, glucose intolerance, hypoalbuminemia, weight loss, and anemia

Epidemiology[2,3] : - Annual incidence of glucagonoma is about 0.1-1 new cases per 1 million
- Representing 1 % of all pancreatic NETs
- Between ages of 19 and 72 years, typically around 50's.
- Sporadic cases
- Up to 20 % associated with multiple endocrine neoplasia syndrome type 1 (MEN1), occur in 3% of MEN1

Clinical Features : The patients are diagnosed late when the disease has metastasized

Necrolytic migratory erythema (NME)[4,5]

- 90% of patients
- Result from malnutrition and amino acid deficiency
- Erythematous papules or plaques involving the face, perineum, and extremities following by blistering, crusting, and scaling at the borders
- Affected areas are often pruritic and painful
- Zinc deficiency, pellagra, kwashiorkor, end-stage liver disease, toxic epidermal necrolysis, pemphigus foliaceus, and pustular psoriasis should be excluded
- Diagnosis from skin biopy --> superficial necrolysis with separation of the outer layers of the epidermis and perivascular infiltration with lymphocytes and histiocytes

Weight loss : 80% of patients[4], consequence of the catabolic actions of glucagon

Diabetes mellitus : 40% of patients[4], mild and nonketotic

Venous thrombosis : 30% of patients, manifests as deep vein thrombosis or pulmonary embolism[6]

Others: Chronic diarrhea, neuropsychiatric manifestations, dilated cardiomyopathy, anemia

Diagnosis

- Clinical with necrolytic migratory erythema with or without associated weight loss, glucose intolerance, chronic diarrhea, or venous thrombosis with serum glucagon > 500 pg/mL[4]

- Serum glucagon > 1,000 pg/mL[8]

- Conditions other than glucagonoma that can induce moderate elevations in the serum glucagon concentration (<500 pg/mL) include hypoglycemia, fasting, trauma, sepsis, acute pancreatitis, abdominal surgery, Cushing's syndrome, and renal and hepatic failure[4]

- Histologic diagnosis by biopsy is not required to make the diagnosis

Tumor Localization

CT scan [9-11]: - Noninvasive and highly accurate for detecting pNETs

- Sensitivity >80 %

- Intravenous contrast enhances the detection of lesions during the arterial phase

MRI[12]: - Typically characterized by low signal intensity on T1-weighted images and high signal intensity on T2-weighted images

- Higher sensitivity for liver metastases as compared with CT

Somatostatin-receptor scintigraphy (OctreoScan)[14]

- Use radiolabeled octreotide

- Detection of metastases outside of the abdominal region

Endoscopic ultrasound[13]

- Rarely used in the evaluation of glucagonomas

- Detect pancreatic tumours as small as 2–3 mm

- Provides accurate information on the local extent of disease

- Allows transmucosal needle biopsy of pancreatic lesions

Angiography[15]

- Invasive testing

- Reserved for patients who are strongly suspected but imaging is negative

Positron emission tomography (PET)

- Functional imaging

- Improved sensitivity for detection of small lesions

Staging and Grading system

Table 1 TNM staging for exocrine and endocrine tumors of the pancreas[16]

Primary tumour (T stage)		Lymph nodes, regional (N stage)		Distant metastasis (M stage)	
Tx	Cannot be assessed	Nx	Cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumour	N0	No metastasis	M1	Distant metastasis
Tis	Carcinoma in situ: PanInIII	N1	Lymph node metastasis		
T1	Limited to the pancreas, <2 cm				
T2	>2 cm but limited to pancreas				
T3	Tumour extended from the pancreas but no involvement of celiac axis or SMA				
T4	Unresectable, celiac axis, or SMA involvement				

SMA superior mesenteric artery

Table 2 Grading Systems for Gastroenteropancreatic Neuroendocrine Tumors[23-25]

Differentiation	Grade	Gastroenteropancreatic Neuroendocrine Tumors (ENETS, WHO)
Well differentiated	Low grade (G1)	< 2 mitoses / 10 hpf AND < 3% Ki67 index
Well differentiated	Intermediate grade (G2)	2-20 mitoses / 10 hpf OR 3%-20% Ki67 index
Poorly differentiated	High grade (G3)	> 20 mitoses / 10 hpf OR > 20% Ki67 index

Treatment

Initial management : Supportive care and management of glucose intolerance/diabetes

Medication: Somatostatin analogs (Octreotides)[18]

- Control symptoms related to glucagon hypersecretion
- Inhibit hormone secretion
- Reducing serum glucagon concentrations

Surgery

1. **Pancreatic resection**[19,20]
   - Offers the chance of complete cure
   - Cure rate 30%
   - Rapid resolution of hyperglucagonemia and NME usually result after resection
2. **Hepatic resection**[4,21]
   - Treatment of metastatic liver disease
   - Increase survival and has the benefit from symptom palliation
   - Reductions in serum glucagon concentration and in the severity of NME

Hepatic artery embolization[22]

- Palliative technique in patients with symptomatic hepatic metastases
- Not candidates for surgical resection
- With or without chemotherapy

Radiofrequency ablation and cryoablation

- Adjunct to surgical resection
- Percutaneous or laparoscopic
- Less invasive

Molecularly targeted therapy: everolimus, sunitinib

- Progressive advanced glucagonomas
- Rapidly progressive metastatic disease

Cytotoxic chemotherapy: streptozocin-based combination or temozolomide-containing regimen

- Initial treatment together with a somatostatin analog
- Rapidly enlarging metastases
- Limited data

Prognosis and Follow-Up

- Unpredictable prognosis

- Rarely cure in metastasis disease

Table 3 5- and 10-year survival rates for resected pancreatic neuroendocrine tumour patients[17]

Stage		Observed survival		Median survival (months)
		5 years (%)	10 years (%)	
T1N0M0	Stage 1A	61.0	46.0	112
T2N0M0	Stage 1B			
T3N0M0	Stage IIA	52.0	28.8	63
T1N1M0 T2N1M0 T3N1M0	Stage IIB			
T4 anyN M0	Stage III	41.4	18.5	46
Any T and any N M1	Stage IV	15.5	5.1	14

In the long term follow up

- Followed with history and physical examination with tumour markers every 6–12 months for years 1–3, and as clinically indicated thereafter

- Imaging studies are recommended as clinically indicated

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