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A REVIEW ON 4D GLUCAGONOMA SYNDROME

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ABSTRACT
4D Syndrome is a term used to describe a manifestation of syndromic Glucagonomas, a type of Pancreatic endocrine tumor. According to WHO classification of tumors of the digestive system, glucagonoma is a type of functional pancreatic neuroendocrine neoplasm(pNEN) This pancreatic neuroendocrine tumor(pNET) secretes glucagon and causes a combination of symptoms known as glucagonoma syndrome. Glucagonoma is an extremely rare pancreatic alpha-islet cell tumor and is often accompanied by certain clinical symptoms including necrotizing migratory erythema (NME), diabetes, weight loss and anemia.[3] In 75-80% of cases, the glucagonoma starts in malignant form, and in 50% of these cases, metastasis exsists at diagnosis. Diagnosis is elevated glucagon levels. Tumor is localized with CT and endoscopic ultrasonography.[5] The treatment include where the tumor is, its size and whether it has spread(stage). Surgery includes thev removal of –just the tumor(enucleation), the narrowest part of the pancreas and the body of the pancreas(distal pancreatectomy), the whole of the pancreas(total pancreatectomy), the widest part of the pancreas, duodenum, gallbladder and part of the bile duct(pylorus preserving pancreaticoduodenectomy or PPPD for short), the widest part of the pancreas, duodenum, gallbladder, part of the bile duct and part of the stomach(whipple s operation). Some drugs cause partial regression of NME, In the literature good results have been obtained with streptozotocin+/doxorubicin or 5-fluorouracil, Sunitinib was approved by FDA for PNET, Lanreotide(somatuline depot) has been given for metastatic gastroenteropancreatic neuroendocrine tumors(GEP-NETs), to improve progression – free survival.[19]

KEYWORDS: Glucagonoma, pNEN, pNET, GEP-NET, Enucleation.

INTRODUCTION

DEFINITION

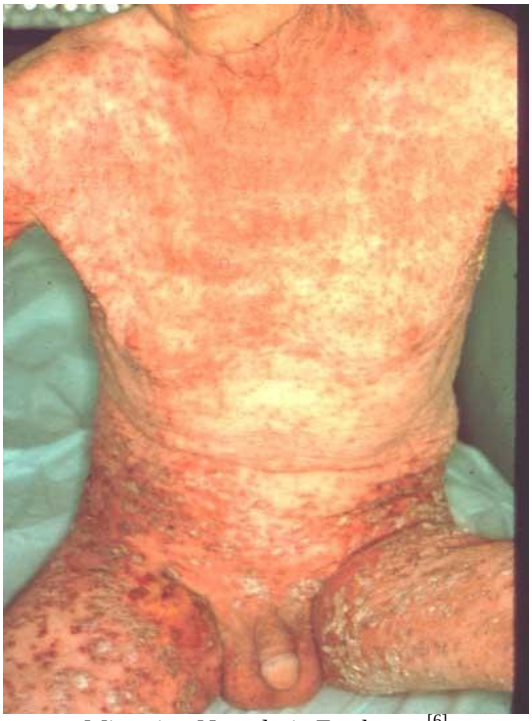
4D Syndrome is also known as Glucagonoma. Glucagonoma is a rare neuroendocrine tumor involving the pancreas.[4] Glucagon is a harmone produced by the pancreas that works with insulin to control the amount of sugar in the bloodstream. It is characterized by tumor cells that produce large amounts of glucagon, and these high levels create severe, painful, and life-threatening symptoms.[5] [10]

The 4D Syndrome is characterized by four ‘D’s as follows-

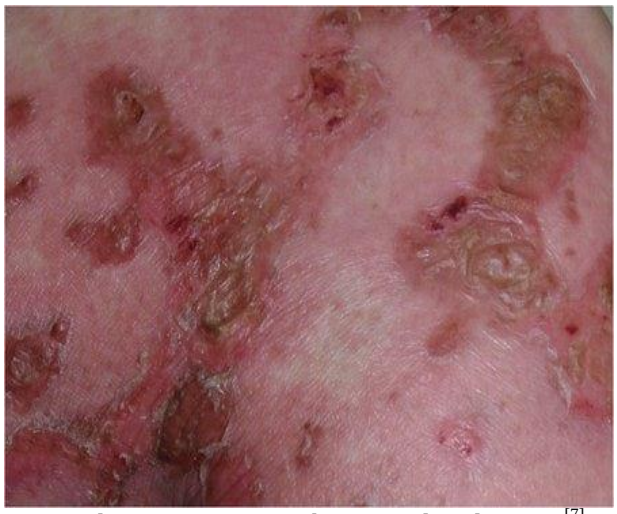
1. Dermatitis: necrolyticmirgratory erythema- a widespread rash, tending to involve perioral and perigenital regions
2. D: mild diabetes mellitus
3. D: deep vein thrombosis
4. D: depression-may be related to severe chronic dermatosis.[1]

NECROLYTIC MIGRATORY ERYTHEMA

NEM is a red, blistering rash that spreads across the skin. It particularly affects the skin around the mouth and distal extremities; but may also be found on the lower abdomen, buttocks, perineum, and groin, heals with hyperpigmentation but without scarring in 7-14 days. It is strongly associated with glucagonoma.[7]



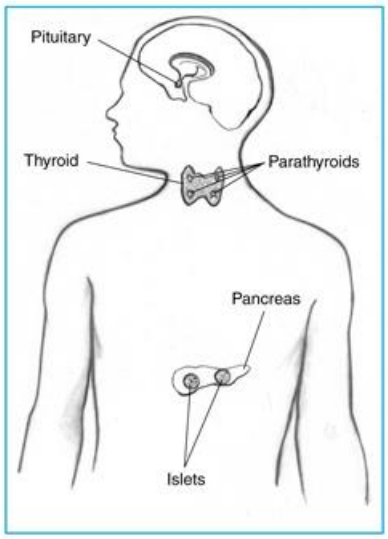
Migrating Necrolytic Erythema.[6]



Necrolytic Migratory Erythema in Gluteal region.[7]

MULTIPLE ENDOCRINE NEOPLASIA

Multiple endocrine neoplasia is of different types i.,e MEN type-1. MEN 2A, MEN 2B of which MEN-1 is the cause of glucagonoma. MEN 1 is a hereditary syndrome characterized by hyperplasia or sometimes adenomas of the parathroid glands, pancreatic islet cell tumors(also known as pancreatic neuroendocrine tumors).[8]



In MEN 1, the overactive glands may include the parathyroids, pancreas or pitutory.[9]

ETIOLOGY

-The causes of glucagonoma are currently unknown.
-In most cases it is suspected that genetic factors play a strong role.
-Having family members with MEN 1
-Mahvash disease
-Niacin deficiency
-Diabetes mellitus

EPIDEMIOLOGY

Glucagonoma is a rare, functioning type of pancreatic neuroendocrine tumor with the estimated incidence in the general population is 1/20,000,000[11] and with an annual incidence of 0.01 to 0.1 new cases per 1,00,000. Glucagonomas are usually solitary, and the majority are located in the distal pancreas. While most glucagonomas are sporadic, up to 20 percent may be associated with MEN 1. However, glucagonomas occur in only 3% of MEN-1 patients.[12]

No race prevalence is known for glucagonoma. The frequency of glucagonoma in males and females is nearly equal, although a greater incidence has been reported in females. Most patients with glucagonoma are in the fifth decade of life, with a mean age of 55 years and an age range of 19-84 years.[4]

SIGNS AND SYMPTOMS

-Blood sugar, symptoms are same as the symptoms of diabetes
-Weight loss
-Normochromic anemia
-Hypoaminoacidemia
-Hypolipidemia
-Chronic eruption involving the extremities, often associated with a smooth, shiny, vermilion tongue and cheilitis

-The exfoliating, brownish red, erythematous lesion with superficial necrolysis is termed necrolytic migratory erythema.[15]

PATHOPHYSIOLOGY

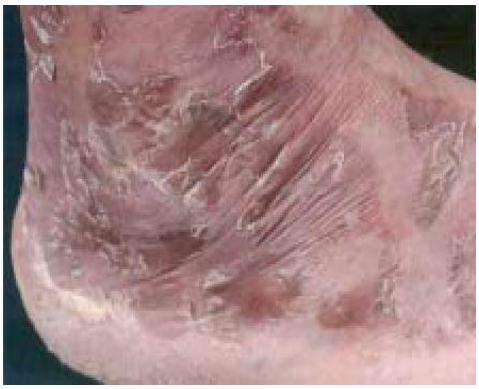
Glucagonoma syndrome is thought to be directly related to elevated glucagon levels. Glucagon is a single-chain polypeptide made up of 29 aminoacids that are derived from a larger precursor peptide, which is cleaved upon secretion. The main site of glucagon production is pancreatic alpha-islet cells, which secrete glucagon in response to hypoglycemia, amino acids, gastric inhibitory peptide, and ghrelin.

Glucagon acts in the liver to increase glycogenolysis and gluconeogenesis by stimulating the cAMP pathway resulting in an elevation of plasma glucose. The secretion of glucagon is inhibited by hyperglycemia, insulin, somatostatin, and GLP-1. It also causes relaxation of the smooth muscle of the stomach, duodenum, small bowel, and colon. The other actions of glucagon include stimulation of lipolysis.

Excessive secretion of glucagon from the tumor leads to the Glucagonoma syndrome. Classic glucagonoma syndrome consists of weight loss, NME, diabetes and mucosal abnormalities including stomatitis, cheilitis, and glossitis. The precise etiology of NME is not known, but it is thought secondary to a combination of poor nutrition, low zinc, and aminoacid levels. Diabetes results secondary to the direct effects of glucagon. Diarrhea may occur from increased glucagon levels and co-secretion of gastrin, serotonin or calcitonin.[13]

CLINICAL MANIFESTATIONS

-Skin rash - usually starts with small circles of redness which develop into itchy, painful bllisters. The rash is called necrolytic migratory erythema(NME). It can affect most parts of the body but is more common in the:
Buttocks
Groin
Back passage(anal area)
The sexual organs such as the penis and vagina(genitals)
Lower part of the legs



NME with typical scaling erythema and hyperpigmentation.[24]

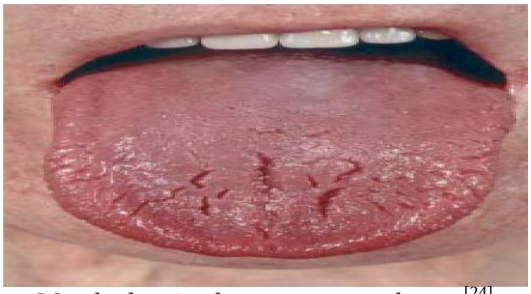
Between 70 and 90 out of every 100 people with glucagonoma (70-90%) have NME.

-Weight loss - you may lose a lot of weight even if you are not on diet. More than 90 out of every 100 people with glucagonoma(more than 90%) lose weight.

-Diabetes - some people have high blood sugar levels. This causes:
Thirst
Passing a lot of urine
Weakness
Weight loss and hunger

Between 40 and 90 out of every 100 people with glucagonoma (40 and 90%) have diabetes.

-Mouth ulcers - you might have broken areas of skin (ulcers) in the mouth that causes pain or discomfort, between 30 and 40 out of every 100 people with glucagonoma (30 to 40%) have a sore mouth.



Mouth ulcer in glucagonoma syndrome.[24]

-Diarrhoea : having more than 3 watery poos (stools) in a 24 hour poeriod. You might also have diarrhoea at night and problems controlling your bowels(incontince).

This happens to about 15 out of every 100 people with glucagonoma(15%)
-Blood clots : Blood clots might develop in the deep veins of the body. This is called deep vein thrombosis(DVT). Symptoms of blood clots include:
Pain, redness & swelling around the area where the blood clot is
The area around the clot may feel warm to touch

Blood clots can also develop in a blood vessel in your lungs. This is a pulmonary embolism(PE). Symptoms of PE include:
Pain in your chest or upper back
Difficulty breathing
Coughing up blood.
-Mood changes: Moood changes include feeling depressed and agitated.
-Low levels of RBCs: Anemia can make you feel very tired and breathless.
It happens in up to 80 out of every 100 people with glucagonoma (80%).

COMPLICATIONS OF GLUCAGONOMA

Excess glucagon leads to diabetes- like symtoms. High blood sugar can cause:
Nerve damage
Blindness
Metabolic problems
Brain damage
Deep vein thrombosis can cause blood clots to travel to the lungs, and it can even cause death.
If the tumor invades the liver, it can eventually cause hepatic failure.[23]

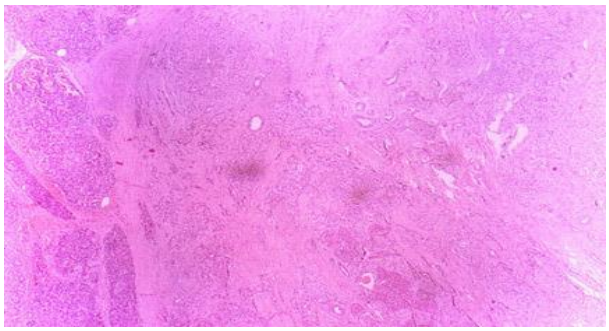
DIAGNOSIS

-Serum glucagon levels - Most patients with glucagonoma have glucagon levels >1000pg/mL (normal is<200pg/mL)
>1000ng/L (normal is <200ng/L)
However, moderate elevations occur in renal insufficiency, acute pancreatitis, severe stress, and fasting.
-Radio immuno assay(RIA) - To determine the level og glucagonemia.
-Fasting and Post pandrial blood sugar levels/ GTT - To establish the presence of Diabetes
-Serum concentrations of aminoacids and zinc - To evaluate the nutritional status.
-The serum levels of Blood chromogranin A(cgA): has been proposed as and demonstrated to be a type of sensitivity marker for determinimg the presence of glucagonoma.
-Complete blood picture (CBP) – To check concurrent normocytic anemia
-A comprehensive metabolic panel (CMP) should be checked to detect other metabolic abnormalities.
-Serum parathyroid harmone, gastrin, insulin, pancreatic polypeptide, serotonin, vasoactive intestinal polypeptide(VIP), prolactin and ACTH levels is important as glucagonoma can rarely be associated with the MEN 1 syndrome.
-Skin biopsy- Skin biopsy of the NME lesion shows small bullae consisting of acantholytic epidermal cells along with lymphocytic and neutrophillic infiltrate. The dermis contains a perivascular lymphocytic infiltrate with an intact epidermis.
-Determining the level of transaminases, bilirubinemia, and alkaline phosphatase is important in order to detect Hepatic metastases.
-Detection of telomerase and the quantification of the human telomerase reverse transcriptase (hTERT) protein subunit have been prposed for distinguishing clinically benign from malignant endocrine tumors.
-Stimulation tests with arginine, secretin, or tolbutamide, which rapidly stimulate plasmatic glucagon levels in patients affected by glucagonoma, areof little additional help.

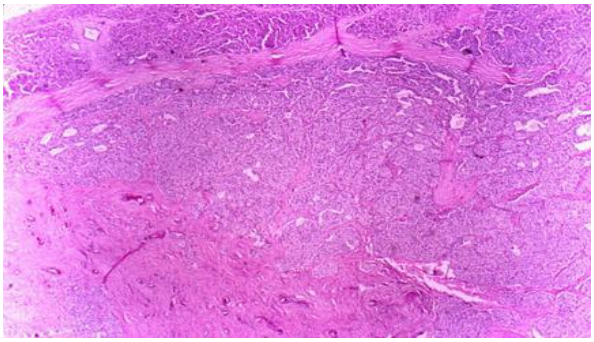
HISTOLOGICAL FINDINGS

Usually, glucagonomas arise from alpha-2 cells of the pancreatic islets and grossly appear as a single mass(80%). In approximately 80% of cases, glucagonoma is a carcinoma, and it is an adenoma in 20% of cases.[4]

Localized in the tail of pancreas
-Glucagonoma is rarely found in a gastric or duodenal location.
-The tumor appears as a solid, single mass of 5cm or more that is well demarcated from the surrounding parenchyma and is capsulated, with a rich network that differentiates it from pancreatic adenocarcinomas.
-The basic skin damage seems to consist of small blisters, which contain acantholytic epidermal cells, neutrophils, and lymphocytes.
-Metastases that are histologically similar to the primitive tumor may be in the liver(60-90%), figures are included below :



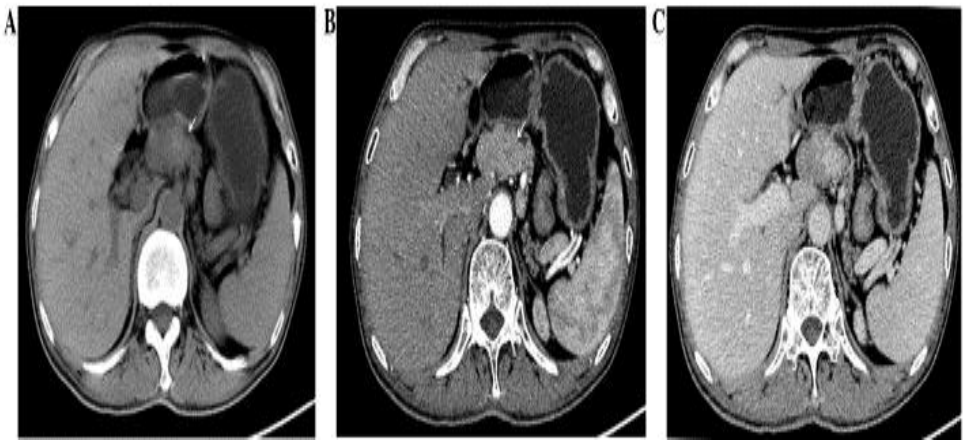
A section of a glucagonoma mass with several fiber bundles and solid cellular strands.



A section of a glucagonoma mass with irregular aspects of fibre bundles and cellular strands.[4]

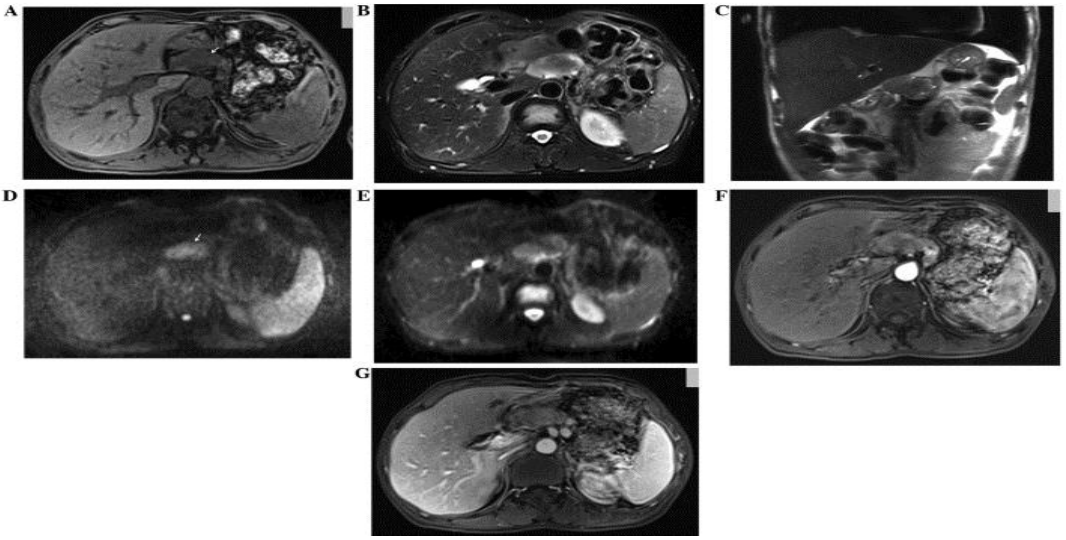
IMAGING STUDIES

Computed tomography(CT)



CT manifestations of glucagonoma syndrome. (A) Plain abdominal CT revealing an obscure mass(arrow) in the neck of the pancreas. The lesion was slightly enhanced during (B) the arterial phase and washed out during (C) the portal venous phase upon enhanced CT.[22]

Magnetic resonance imaging(MRI)

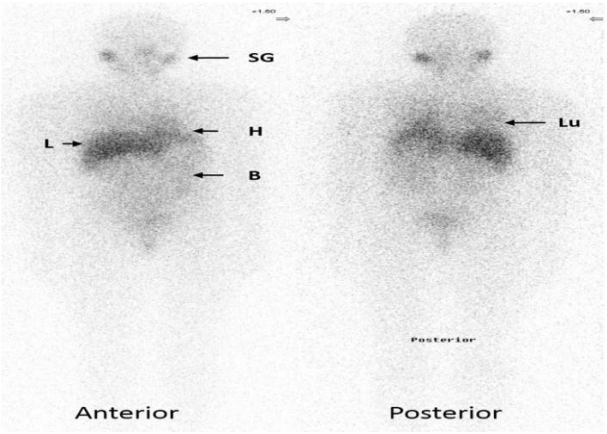


MRI manifestations of glucagonoma syndrome. The lesion exhibited a low signal intensity(arrow) on (A) T1-weighted imaging (WI), and a slightly high signal intensity on (B) T2WI(with fat suppression) and (C) half Fourier acquisition single-shot turbo spin sequence imaging. Diffusion-WI revealing the presence of a lesion with (D and E) heterogenous hyperintensity (arrow), which was mildly reinforced during (F) the arterial phase and washed out during (G) the portal venous phase during enhanced imaging.[22]

Metaiodobenzylguanidine(MIBG) scintigraphy:

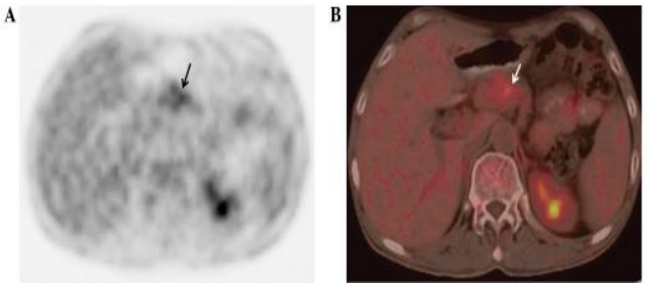
An MIBG scan is a nuclear medicine imaging test. It combines a small amount of radioactive material with a substance called metaiodobenzylguanidine(MIBG) to find certain type of tumors in the body.

An MIBG scan may also be called MIBG scintigraphy or MIBG scintiscan.



^{131}I-MIBG scan showing physiological tracer uptake in SG, H, L, B and diffuse uptake in Lu. B, bowel; H, heart; L, liver; Lu, lungs; SG, salivary glands.[16]

Positron emission tomography(PET)



PET-CT manifestations of glucagonoma syndrome. (A and B) PET-CT revealing the presence of a lesion with mild F-fludeoxyglucose uptake (arrow), which corresponds to the location of the tumor identified by CT and MRI.[22]

DIFFERENTIAL DIAGNOSIS

Differential diagnosis include familial hyperglucagonemia, autoimmune and hereditary chronic pancreatitis, Mahvash disease, acrodermatitis enteropathica and cirrhosis.

Fasting plasma glucagon levels may be elevated in other conditions like acute trauma, diabetes mellitus, burn injury, sepsis, renal failure, cirrhosis, pancreatitis or cushing syndrome. Though the fasting plasma glucagon levels in these conditions are elevated, it is typically less than 500pg\mL. A rare disorder due to an inactivation mutations defect in the glucagon receptor gene that causes pancreatic alpha cell hyperplasia, an elevation of glucagon without symptoms is called Mahvash disease.

NME is not specific to glucagonoma and can also be seen in with chronic liver disease, inflammatory bowel disease, pancreatitis, heroine abuse, jejunal and rectal adenocarcinoma, and myelodysplastic syndrome.

NME-like lesions have been associated with essential fatty acid deficiency, zinc deficiency(acrodermatitis enteropathica), and the dermatosis of protien-calorie malnutrition.[13]

GLUCAGONOMA STAGING

According to The American Joint Committee on Cancer(AJCC), there are four stages of glucagonoma based on the TNM staging system.

T	Primary Tumor
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the pancreas, <2 cm in greatest dimension
T2	Tumor limited to the pancreas, >2cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery(unresectable primary tumor)

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M	Distant Metastases
M0	No distant metastasis
M1	Distant metastasis

Anatomic stage/Prognostic Groups

Stage	T	N	M
0	Tis	N0	M0
1A	T1	N0	M0
1B	T2	N0	M0
2A	T3	N0	M0
2B	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
3	T4	Any N	M0
4	Any T	Any N	M1

TREATMENT

Targeted therapy- It is a type of treatment that uses drugs or other substances to identify and attack specific cancer cells without harming normal cells. It is employed in the treatment of pancreatic NETs.

1. Empiric immediate-release Octreotide starting dose was 50mcg IV twice a day and a rapid titration (1 week) to 200mcg TID over the course of 1 week.

However, Octreotide has been reported to improve NME in patients without glucagonoma, demonstrating that response is independent of glucagon levels. The first step of treatment is to correct the underlying pathology. Octreotide should be considered as second line of treatment. Recommended starting with a low dose of immediate-release octreotide, and increase for a maximum dose of 200mcg TID. This dose can be maintained until resolution of symptoms and then switched to long-acting release octreotide.[17]

2. Peptide receptor radionuclide therapy(PRRT): 177Lu DOTATATE – First-line therapy in patients with glucagonoma and secreting metastasis.

3. Patients with glucagonoma who have severe weight loss may require a period of total parenteral nutrition as part of the preoperative preparation.

Antibiotics, steroids, aminoacids, and zinc supplementation may improve severe skin rash.

4. Patients for whom surgery is not feasible, consider administering
Streptozotocin
Doxorubicin or Streptozotocin
5-fluorouracil

5. Patients with widespread metastases, consider hepatic artery catheterization for infusion of Doxorubicin, cisplatin, and mitomycin-c.

METASTASIS THERAPY

Hepatic artery embolization

-Hepatic artery embolization is palliative treatment in patients with symptomatic hepatic metastases who are not candidates for surgical resection.
-Embolization can be performed via infusion through an angiography catheter into hepatic arteries.

Radiofrequency ablation-The use of a special probe with tiny electrodes that kill cancer cells. Sometimes, the probe is inserted directly through the skin and only local anesthesia is needed. In other cases, the probe is inserted through an incision in the abdomen. This is done in the hospital with general anesthesia.
-Ablation can be performed percutaneously or laproscopically in patients with symptomatic hepatic metastases who are not candidates for surgical resection.
-Ablation is applicable only to smaller lesions less than 3cm.

Molecular therapy- Sunitinib is radio-labelled somatostatin analog which has a role in the management of glucaganoma's that are not symptomatic or have rapily progressive metastasis.

SURGERY

Management of primary disease

Surgery is the mainstay of treatment for glucagonoma. The feasibility of surgery depends on the stage of glucagonoma at diagnosis. Hepatic resection is indicated for the treatment of metastatic liver disease in patients who are candidates for surgery with no extensive extrahepatic metastases.

-Resection of the primary pancreatic tumor is indicated if the tumor is indicated if the tumor is resectable in good general condition patients. It offers the chance of complete cure.
-Preoperative management; total parenteral nutrition may be required before the surgery. Infusions of aminoacids and fattyacids reduce symptoms and improve survival rates
-Single, small lesion in head or tail of pancreas: Enucleation, if feasible
-Large lesion in the head of the pancreas that is not amenable to enucleation: pancreaticduodenectomy
-Single, large lesion in body/tail: distal pancreatectomy
-Multiple lesions: Enucleation, if feasible

Enucleation- Surgery to remove the tumor only. This may be done when cancer occurs in one place in the pancreas.

Pancreaticduodenectomy- A surgical procedure in which the head of the pancreas, the gallbladder, nearby lymph nodes and part of the stomach, small intestine, and bile duct are removed. Enough of the pancreas is left to make digestive juices and insulin. The organs removed during this procedure depend on the patient's condition. This is also called the Whipple's procedure.

Distal pancreatectomy- Surgery to remove the body and tail of the pancreas. The spleen may also be removed if cancer has spread to the spleen.

Management of metastasis
Hepatic resection is indicated for the treatment of metastatic liver disease in patients who are candidates for surgery with no extensive extrahepatic metastases. It may potentially increases survival and has the benefit of symptom palliation.

PREVENTION
-Currently there are no defenitive methods available to prevent Glucagonoma Syndrome.
-Individuals who have a family history of Multiple neuroendocrine neoplasia type 1 (MEN 1) may benefit from genetic counselling.
-Active research is currently being performed to explore the possibilities for treatment and prevention of inherited and acquired genetic disorders.[21]

REFERENCES

1. Dr Ayla Al Kabbani and Dr Matt A. Morgan et al., 4D Syndrome. Radiopaedia.org 2005-2020 https://radiopaedia.org/articles/4d-syndrome-1
2. Juraj Hegyi et al., Pellagra: Dermatitis, Dementia, and Diarrhea. Int J Dermatol, Jan 2004; 43(1): 1-5. https://pubmed.ncbi.nlm.nih.gov/14693013/
3. Xujun Song,* Suli Zheng,* Gang Yang,* Guanbing Xiong, Zhe Cao, Mengyu Feng, Taiping Zhang, and Yupei Zhao. Glucagonoma and the glucagonoma syndrome. Oncol Lett., Mar 2018; 15(3): 2749-2755. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5778850/
4. Ricardo R Correa Marquez, MD, EsD, FACP, FACE, FAPCR, CMQ, ABDA, FACHT. Glucagonoma. Mar 2020 https://emedicine.medscape.com/article/118899-overview#a1
5. Minhhuyen Nguyen, MD, Fox Chase Cancer Center, Temple University. Glucagonoma; Jun 2019 https://www.merckmanuals.com/professional/gastrointestinal-disorders/tumors-of-the-gastrointestinal-tract/glucagonoma
6. Aaron Vinik, MD, PhD, FCP, MACP, FACE. Karel Pacak, MD, PhD, DSc, FACE. Eric Feliberti, MD, FACS, and Roger R Perry, MD., FACS. Glucagonoma Syndrome; Hune 2017 https://www.ncbi.nlm.nih.gov/books/NBK279041/
7. Eduardo P. Gracia del Valle. Necrolytic migratory erythema https://en.m.wikipedia.org/wiki/Necrolytic_migratory_erythema
8. Patricia A. Daly, MD, University of Virginia; Lewis Landsberg, MD, Northwestern University Feinberg school of medicine. Overveiw of Multiple Endocrine Neoplasias(MEN). Mar 2019 https://www.msdmanuals.com/professional/endocrine-and-metabolic-disorders/multiple-endocrine-neoplasia-men-syndromes/overview-of-multiple-endocrine-neoplasias-men
9. White ML, Doherty GM. Multiple endocrine neoplasia. Surgical Oncology Clinics of North America. 2008; 17: 439-459. https://www.niddk.nih.gov/health-information/endocrine-diseases/multiple-endocrine-neoplasia-type-1
10. Diabetes. Co. uk- the global diabetes community. Glucagonoma. 2003-2020 Diabetes Digital Media Ltd[online] https://www.diabetes.co.uk/glucagonoma.html
11. Dr Run YU et al., Glucagonoma. Nov 2014 https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=97280
12. Emily Bergsland, MD et al., Glucagonoma and the glucagonoma syndrome; Mar 2019 https://www.uptodate.com/contents/glucagonoma-and-the-glucagonoma-syndrome#H3
13. Sartaj Sandhu; Ishwarlal Jailal. VA medical center, MATHER, CA. Glucagonoma Syndrome. Nov 27, 2019 https://www.ncbi.nlm.nih.gov/books/NBK519500/#_article-22304_s4_
14. Cunha-Silva, M., Costa, J., Faria, G., Massuda, J., Cintra, M., Costa, L., Assad, V., Ataide, E., Mazo, D., & Seva-Pereira, T. (2019). Diarrhea: a missed D in the 4D glucagonoma syndrome. Autopsy and case reports, 9(4): e2019129. http://www.revistas.usp.br/autopsy/article/view/164486
15. Cancer Research UK. Symptoms of glucagonoma; 25 Jun 2019.

https://www.cancerresearchuk.org/about-cancer/neuroendocrine-tumours-nets/pancreatic-nets/glucagonoma/symptoms

16. Archi Agarwal, MBBS, DMRE, DRM, DNB, Venkatesh Rangarajan, MBBS, DRM, DNB, Sneha Shah, MBBS, DRM, DNB, Ameya Puranik, MBBS, DNB, and Nilendu Purandare, MBBS, DMRD, DNB. MIBG(Metaiodobenzylguanidine) theranostics in pediatric and adult malignancies. BrJ Radiol, 2018 Nov; 91(1091): 20180103 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6475939/
17. Franco Vallejo Garcia, MD and Valentina Rodriguez, MD. Sun-323 Somatostatin Analogue: An Effective Treatment for Pseudoglucagonoma Syndrome, J Endocr Soc., 2019 Apr 15; 3(suppl 1): SUN-323. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6552871/
18. C. Michael Gibson, M.S., M.D. Parminder Dhingra, M.D. Mohammed Abdelwahed M.D. Glucagonoma staging. https://www.wikidoc.org/index.php/Glucagonoma_staging
19. UCSF Department of Surgery. General information about pancreatic neuroendocrine tumors.https://surgery.ucsf.edu/conditions--procedures/pancreatic-neuroendocrine-(islet-cell)-tumors.aspx
20. Emilio Bombardieri et al., $^{131}I/^{123}I$-Metaiodobenzylguanidine(mIBG) scintigraphy: procedure guidelines for tumor imaging. Eur J Nucl Mol Imaging, 2010; 37: 2436-2446. http://snmmi.files.cms-plus.com/docs/hpra/2010_published_OC_131I_123I_Metaiodobenzylguanidine_Scintigraphy.pdf
21. Glucagonoma: Symptoms, causes and prevention. https://www.google.com/amp/s/diseasesdic.com/glucagonoma-symptoms-causes-and-prevention/amp/
22. WEI-FU LV, JIAN-KUI HAN, XIN LIU, SHI-CUN WANG, BO PAN and AO XU. Imaging features of glucagonoma syndrome: A case report and review of the literature: 2015 Apr; 9(4): 1579-1582. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4356379/
23. Christine Case-Lo, Steve Kim, MD: Glucagonoma, 22, 2016 https://www.google.com/amp/s/diseasesdic.com/glucagonoma-symptoms-causes-and-prevention/amp/amp
24. A.P. Van Beek, E.R.M. de Haas : The glucagonoma syndrome and necrolytic migratory erythema: A clinical review, November 2004; 151(5): 531-7. https://www.researchgate.net/figure/Glossitis-in-the-glucagonoma-syndrome_fig3_51369927