

GLUCAGON & GLUCAGONOMA SYNDROME

Wouter W. de Herder, MD, PhD, Professor of Endocrine Oncology, Department of Internal Medicine, Division of Endocrinology, Erasmus Medical Center and Erasmus MC Cancer Institute, Rotterdam, the Netherlands. w.w.deherder@erasmusmc.nl

Johannes Hofland, MD, PhD, Endocrinologist, Department of Internal Medicine, Division of Endocrinology, Erasmus Medical Center and Erasmus MC Cancer Institute, Rotterdam, the Netherlands. j.hofland@erasmusmc.nl

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ABSTRACT

The glucagonoma syndrome is caused by a glucagon-secreting pancreatic neuroendocrine neoplasm (panNEN)(glucagonoma). The syndrome includes: necrolytic migratory erythema, painful glossitis, cheilitis & stomatitis, weight loss, anemia, new-onset or worsening diabetes mellitus. hypoaminoacidemia, low zinc levels, deep vein thrombosis and depression. At diagnosis, a glucagonoma is usually larger than 4-5 cm in diameter and locoregional lymph node and distant metastases, particularly to the liver or bones are present. The incidence of glucagonoma syndrome is 1-2% of all panNENs. Approximately 10% of associated glucagonomas are with multiple endocrine neoplasia type 1 (MEN1). Glucagonomas highly express somatostatin receptor subtypes and, therefore, somatostatin receptor positron emission tomography (PET) CT/MRI with ⁶⁸Ga- labelled somatostatin analogs (DOTATATE, DOTANOC, and DOTATOC) can be used in the localization of glucagonomas. The somatostatin receptor subtypes can also be utilized for peptide receptor radionuclide therapy with radiolabeled somatostatin analogs of metastatic glucagonomas. Other treatment options include supportive measures like amino acids, surgery, somatostatin analogs, sunitinib, everolimus,

systemic cytotoxic chemotherapy, and liver-directed therapies. Glucagon cell hyperplasia and neoplasia of the endocrine pancreas is an autosomal recessive syndrome associated with hyperglucagonemia and is a genetically determined receptor disease, affecting the glucagon receptor. Patients with this disorder can develop multiple glucagonomas. However, the clinical presentation is NOT with the glucagonoma syndrome.

INTRODUCTION

Glucagon is a 29-amino acid polypeptide hormone with a molecular mass of 3485 daltons, which is produced by alpha cells of the pancreas. Glucagon regulates not only glucose, but also amino acid and lipid metabolism. There is substantial evidence in humans that glucagon can also be produced outside the pancreas (1). A glucagonoma is a neuroendocrine neoplasm (NEN) secreting glucagon and pre-pro-glucagon-derived peptides.

HISTORY

In 1923, a hyperglycemic factor named "glucagon" was isolated from beef pancreas in Rochester, NY, USA by the biochemistry student Charles P. Kimball

(1897-19..) and his mentor John R. Murlin (1874-1960) (2-5). In 1942, the US dermatologist S. William Becker (1894-1964) and colleagues were the first to describe the typical glucagonoma skin eruption in a patient with a pancreatic tumor (6). In 1963, Roger Unger and colleagues succeeded in recovering glucagon from extracts of pancreatic endocrine tumors found at autopsy (7). In 1966, the US pathologist Malcolm H. McGavran (1923-1999) and his associates published the first report on a patient with a glucagonoma (5,8). This 42-year-old woman presented with diabetes mellitus, anemia, a peculiar skin eruption and a metastatic pancreatic tumor. Later in the course of the disease, elevated plasma glucagon levels were found (8). The tumor was biopsied and operated by the US surgeon Hiram C. Polk Jr.(8). The characteristic cutaneous lesion which occurs in association with the glucagonoma syndrome was first described by the British dermatologist Ronald E. Church (1922-2007) and his colleague, the pathologist Walter (Bill) A.J. Crane (1925-1982) (9). The British dermatologist Darrell S. Wilkinson (1919-2009) named this lesion "necrolytic migratory erythema" (NME) in 1971 (5,10). In 1974, the British gastroenterologist Christopher Ν. Mallinson in collaboration with Stephen R. Bloom and colleagues described four glucagonoma patients with the glucagonoma syndrome and NME with increased plasma glucagon levels and very low plasma amino acid concentrations (11). One patient fully recovered after resection of the glucagonoma (5,11). In the same year, a similar complete response of the glucagonoma syndrome and NME after surgical resection was described by the British dermatologist R. Douglas Sweet (1917-2001)(5,12). The first welldocumented cases of glucagon cell hyperplasia and neoplasia (GCHN) of the endocrine pancreas (Mahvash syndrome) were published in 2006 by the German pathologist Martin Anlauf and colleagues

(13). The first clinically well-characterized case of GCHN was described by the group of the US-Chinese endocrinologist Run Yu in 2008 (14).

CLINICAL PRESENTATION

The majority of patients with a glucagonoma presents with new onset or worsening of diabetes mellitus (70%) accompanied by significant weight loss (60%), because glucagon hypersecretion has a catabolic effect in combination with diarrhea (15). Other symptoms include painful glossitis (Figure 1), cheilitis & angular stomatitis (41%), onychodystrophy (in females), deep vein thrombosis & pulmonary embolism (16-18), normochromic normocytic anemia (50%), hypoaminoacidemia and low plasma zinc levels (15,19,20). In rare cases, glucagonomas are associated with dilated cardiomyopathy that can be reversible after tumor control (21,22). However, the most distinct symptom in glucagonoma patients concerns skin lesions named necrolytic migratory erythema (NME) which occurs in 80% of patients (23-27). The NME has a characteristic distribution. It is usually widespread with major sites of involvement at the perioral and perigenital regions along with the fingers, legs, and feet (28). The rash starts as an erythematous lesion, progresses to form a bullous which ulcerates forming a depressed lesion that is surrounded by brown pigment (Figure 2). Patients can suffer from itchy or painful lesions. The basic process in the skin seems to be one of superficial epidermal necrosis, fragile blister formation, crusting, and healing with hyperpigmentation (17). Different stages of the cutaneous lesions may be present simultaneously (17). A painful glossitis manifested by an erythematous, mildly atrophic tongue has been associated with the cutaneous lesions (Figure 1).



Figure 1. Glossitis in a glucagonoma patient. Picture included with the informed consent of the patient.



Figure 2. Necrolytic migratory erythema in a glucagonoma patient. Pictures included with the informed consent of the patient.



The typical clinical presentation of glucagonoma is with a tumor size larger than 4-5 cm in diameter and metastatic dissemination has already occurred, particularly in the locoregional lymph nodes, liver, and bones (19,29). Secondary, or metachronous glucagon secretion in panNENs which previously were non-secreting, or secreted other peptide hormones, can also occur and is usually associated with a poor prognosis (30,31).

The clinical incidence of glucagonomas is estimated at 1-2% of panNENs and about 1-2 cases per million population (32,33). The average age of patient at diagnosis is 52.5 years, with a slight higher prevalence in females (15). The 10-year survival of a localized (and subsequently surgically resected) glucagonoma is nearly 100%, but decreases to 50% in the presence of metastatic disease (15,28,34,35). The median survival time for glucagonomas is 7.7 years (20,36,37). About 10% of glucagonomas are diagnosed in patients with multiple endocrine neoplasia type 1 (MEN1)(38,39).

GLUCAGON CELL HYPERPLASIA AND NEOPLASIA

A second, however rare, autosomal recessive syndrome associated with hyperglucagonemia is glucagon cell hyperplasia and neoplasia (GCHN) of the endocrine pancreas (*Mahvash* syndrome) (40,41). GCNH is a genetically determined receptor disease, affecting the glucagon receptor (GCGR). GCGR inactivation interrupts glucagon signaling in the liver, leading to disturbed metabolism of glycogen, fatty acids and amino acids. Altered function of the liver cells subsequently results in hyperplastic changes of the glucagon cells of the pancreatic islets, followed by hyperglucagonemia and the development of multiple glucagon producing NENs (41,42). In one GCHN case, a lymph node micro-metastasis was found (42) Patients are middleaged adults who present with non-specific symptoms such as fatigue, abdominal pain, diabetes, or acute pancreatitis. Despite very high serum glucagon levels, none of the GCHN patients with GCGR mutations showed a glucagonoma syndrome, owing to the interrupted signaling of the GCGR. The only reported GCHN patient with a glucagonoma syndrome and NME harbored a wild type GCGR (42)). The pancreatic NEN (panNEN) can be visualized by somatostatin receptor imaging, since the glucagon cells express somatostatin receptor subtypes (43). GCHN follows a benign clinical course for most patients. However, follow-up of the patients is suggested, as the tumors have a metastatic potential. Glucagon also increases hepatic amino acid turnover, and thus lowers postprandial serum amino acid levels. This disturbed amino acid metabolism probably plays the most important role in the development of GCHN. The impaired glucagon signaling in the liver of GCHN patients results in chronically elevated serum amino acid levels which stimulate the secretion and proliferation of glucagon cells, leading to hyperglucagonemia, glucagon cell hyperplasia, and finally to NENs.

GLUCAGONOMA DIAGNOSIS

The diagnosis of the glucagonoma syndrome is based on the combination of elevated plasma glucagon levels and glucagonoma symptoms as described above. Mild elevated glucagon levels may be associated with several other diseases like cirrhosis, chronic renal failure, sepsis, acute or chronic pancreatitis. chronic hepatic failure. Cushing's syndrome, acute trauma, diabetes mellitus, diabetic ketoacidosis, stress. burns, portocaval NENs shunting, other and familial

hyperglucagonemia (44). However, a fasting plasma glucagon >500 pg/ml (reference range, 70–160 pg/ml) is diagnostic for glucagonoma (45).

Anatomic and functional imaging modalities are important in the localization of a glucagonoma. As in other NENs, 3-phase CT or MRI scans must be performed for the precise localization of these tumors in the pancreas. Since glucagonomas express high numbers of different somatostatin, somatostatin receptor imaging has been used to detect distant metastases and scan-positivity has been reported in up to 97% of glucagonoma patients, (35,46). Currently, positron emission tomography (PET)-CT with ⁶⁸Ga-labelled somatostatin analogs (SSAs) (DOTATATE, DOTANOC, DOTATOC) has the highest sensitivity for detecting metastases of G1-2 and some G3 pancreatic neuroendocrine tumors (panNETs) (47). In line with the work-up for all NENs, a biopsy is advised to confirm the diagnosis and for grading (Ki67 index), as the grade can influence treatment selection (48). An overview of the current staging and grading systems is provided in the chapter "Insulinoma" (49). Tumor cells are positive for general neuroendocrine markers, glucagon, and somatostatin receptor subtype 2a. (28). Skin biopsies of NME usually show psoriasiform hyperplasia of the epidermis, pallor of keratinocytes, vacuolated or dyskeratotic keratinocytes, necrosis of the upper epidermis and perivascular inflammation (17).

The diagnosis of glucagonoma relies on the presence of the glucagonoma syndrome and not on glucagon immunoreactivity in tumor cells alone. PanNENs composed of glucagon-immunoreactive cells but lacking symptoms of the glucagonoma syndrome are defined as "non-functioning glucagon-producing PanNENs". They are frequently small and indolent tumors associated with an excellent

prognosis, while glucagonomas are larger and more frequently metastatic neoplasms (50).

TREATMENT OF GLUCAGONOMA

Supportive Measures

Supportive therapy (also initiated before surgery) includes amino acid infusions (51), essential fatty acids, topic or oral zinc therapies, vitamins, minerals, and glucose control (52). Also, anticoagulant therapy has been recommended because of the increased risk of thrombosis (16,17).

Necrotic Migratory Erythema Therapy Response

Almost invariably, the NME resolves after successful removal of a glucagon-producing tumor, even if the rash has been present for several years (25,53). The NME also improves in patients who do not undergo curative resection but are treated with SSAs (54,55), everolimus, or peptide receptor radionuclide therapy (PRRT) with radiolabeled SSAs (56-58). Impressive improvement of the NME with amino acid repletion has also been described (29,51,59).

Surgery

As for all panNENs, surgery is the only curative treatment. In the occasional patient in whom a glucagonoma is discovered while the tumor is locoregionally confined, pancreatic surgery (enucleation, distal pancreatectomy with or without splenectomy, central pancreatectomy, pancreaticoduodenectomy and total pancreatectomy) should be performed to remove the glucagonoma (60,61). Post-surgery, symptoms of the glucagonoma syndrome will resolve within weeks (25). In selected

patients with limited liver metastases an extended surgical resection can also be considered (62). Preoperative preparation is required including correction of malnutrition and hyperglycemia. Somatostatin analogs (SSAs) should be started to reverse the catabolic state and improve the skin rash (63). Prophylactic measures to prevent venous thrombosis, including the use of low-molecular weight heparin, should be applied to all patients during the perioperative period (29).

In case of unresectable metastases, treatment is focused on tumor stabilization and symptom reduction by decreasing the secretion of glucagon. In general, anti-tumor therapy is similar to nonfunctioning panNENs as specific data for glucagonoma is often lacking. The guidelines by ENETS, NANETS and ESMO describe the selection and sequencing of SSAs, targeted therapy, PRRT with radiolabeled SSAs and cytotoxic chemotherapy (29,64,65).

Somatostatin Analogs

SSAs are the first-line palliative treatments to control glucagon secretion and tumor growth (46). In a randomized controlled trial (CLARINET), including G1-2 panNENs, treatment with lanreotide autogel 120 mg every 4 weeks deep sc was associated with significantly prolonged median progression-free survival (PFS) of 38 months versus 18 months for placebo (66). Moreover, SSAs have been reported to decrease the NME (29,56).

Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) with ¹⁷⁷Lu-DOTATATE results in a response rate of 55% for panNENs, with a median PFS of 30 months and median overall survival (OS) of 71 months (67). PRRT with ¹⁷⁷Lu-DOTATATE for the treatment of metastatic glucagonoma has been described in small case series (58,68). The radiological response rate of glucagonomas seems to be comparable to that observed in patients with clinically non-functioning G1-2 panNETs. Of additional value is the high symptomatic response rate (71%) and the increase in quality of life after treatment with ¹⁷⁷Lu-DOTATATE (29,58).

Everolimus

Everolimus is registered for the second-line treatment of G1-2 panNENs based on the result of the RADIANT-3 trial. In this study, 24% of patients had a functioning (= hormone-secreting) panNEN and everolimus treatment was associated with a (statistically not significant) overall survival benefit of 6.3 months (69,70). Everolimus was found to decrease plasma glucagon levels in patients with elevated plasma glucagon levels (71). However, median plasma glucagon levels in these patients were only 1.5 times the upper limit of normal suggesting that they did not suffer from the classical glucagonoma syndrome. Since everolimus can also worsen diabetes mellitus by reducing insulin secretion from the pancreas and inducing insulin resistance, its contribution to the treatment of glucagonoma patients is still unclear (29).

Sunitinib

In a randomized controlled trial in patients with G1-2 panNENs, second-line sunitinib treatment (37.5 mg/day) resulted in an increased progression-free survival by 5.9 months compared to placebo (72,73). In this trial, 5 glucagonoma patients (3%) were enrolled (72). However, the radiological and

symptomatic response for this subgroup of glucagonoma patients was not separately reported (29,72,73).

Chemotherapy

Treatment of 18 glucagonoma patients with streptozotocin (STZ) and 5-fluorouracil (5-FU) resulted in an objective response in 50% of patients (35). Chemotherapy with capecitabine and temozolomide is also effective for the treatment of panNENs, but no specific data for glucagonoma are available (29,74,75).

Liver-Directed Therapy

As severity of the glucagonoma syndrome is associated with tumor burden, reducing liver tumor burden could potentially reduce symptoms of glucagonoma as well. In patients with liver-dominant disease, liver metastases can be resected or treated by bland embolization, radioembolization (SIRT), radiofrequency ablation (RFA), microwave and high-intensity focused cryoablation. ultrasound laser, brachytherapy (HIFU), and irreversible electroporation (IRE) depending on local availability (76).

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