Endotext

GLUCAGONOMA SYNDROME

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ABSTRACT

The glucagonoma syndrome is caused by a glucagon-secreting pancreatic neuroendocrine neoplasm (glucagonoma). The syndrome includes: a characteristic rash termed 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 4-5 cm in size and accompanied by distant metastases, particularly to the liver. The incidence of glucagonoma syndrome is 1-2% of all pancreatic neuroendocrine tumors. Approximately 10% of glucagonomas are associated with multiple endocrine neoplasia type-1 (MEN-1). Glucagonomas highly express somatostatin receptor subtypes (97%) and therefore somatostatin receptor positron emission tomography (PET) with DOTA-labelled somatostatin analogs (DOTATATE, DOTANOC, and DOTATOC) can be used in the localization of glucagonomas. The somatostatin receptor subtypes can also be utilized for the treatment of metastatic glucagonomas with somatostatin analogs or ^{177}Lu-DOTATATE. Other treatment options include sunitinib, everolimus, systemic cytotoxic chemotherapy, and liver-directed therapies.

INTRODUCTION

In 1923, the US physiologists Charles P. Kimball and John R. Murlin isolated glucagon. In 1942 the US dermatologist S William Becker and colleagues were the first to describe the typical glucagonoma skin eruption in a patient with a pancreatic tumor. In 1971, this was named “necrolytic migratory erythema” by the UK dermatologist Darrell Wilkinson. In 1963, the US physician Roger Unger and colleagues isolated glucagon from extracts of pancreatic neuroendocrine tumors. In 1966, the US pathologist Malcolm H. McGavran and his associates published the first report on a 42-year-old woman with glucagonoma who presented with a metastatic pancreatic tumor, skin eruption, diabetes mellitus, anemia, and elevated plasma glucagon levels in the blood (1).

CLINICAL FEATURES

The majority of patients with a glucagonoma present 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 malnutrition resulting from diarrhea (2). Hyperglycemia in the glucagonoma syndrome is associated with tumor size. Other symptoms include painful glossitis (Figure 1), cheilitis & angular stomatitis (41%), onychodystrophy (in females), deep vein thrombosis, pulmonary embolism, normochromic normocytic anemia (50%), hypoaminoacidemia and low zinc levels (2-4). In rare cases, glucagonomas are associated with dilated cardiomyopathy that can be reversible after tumor resection (5, 6).

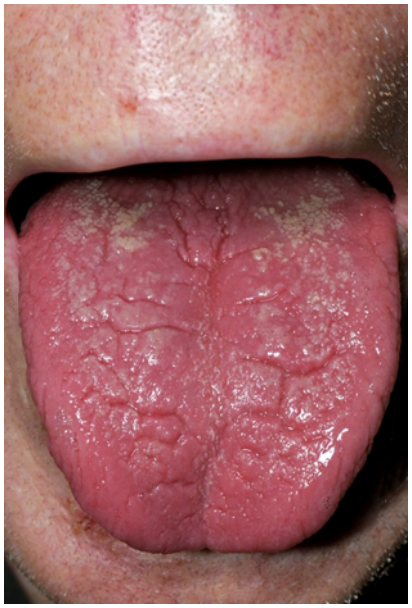

Figure 1. Glossitis in a glucagonoma patient

However, the most distinct symptom in glucagonoma patients concerns skin lesions named necrolytic migratory erythema (NME) which occurs in 80% of patients. The NME rash of the glucagonoma syndrome 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 (7). It may also occur in areas of cutaneous trauma. The rash starts as an erythematous lesion, progresses to form a bullous which ulcerates having a depressed lesion that is surrounded by brown pigment (Figure 2). Patients can suffer from itch or pain at the lesions. The basic process in the skin seems to be one of superficial epidermal necrosis, fragile blister formation, crusting, and healing with hyperpigmentation. Skin biopsies usually show psoriasiform hyperplasia of the epidermis, pallor of keratinocytes, vacuolated or dyskeratotic keratinocytes, necrosis of the upper epidermis and perivascular inflammation (8). Different stages of the cutaneous lesions may be present simultaneously. A painful glossitis manifested by an erythematous, mildly atrophic tongue has been associated with the cutaneous lesions (Figure 1).

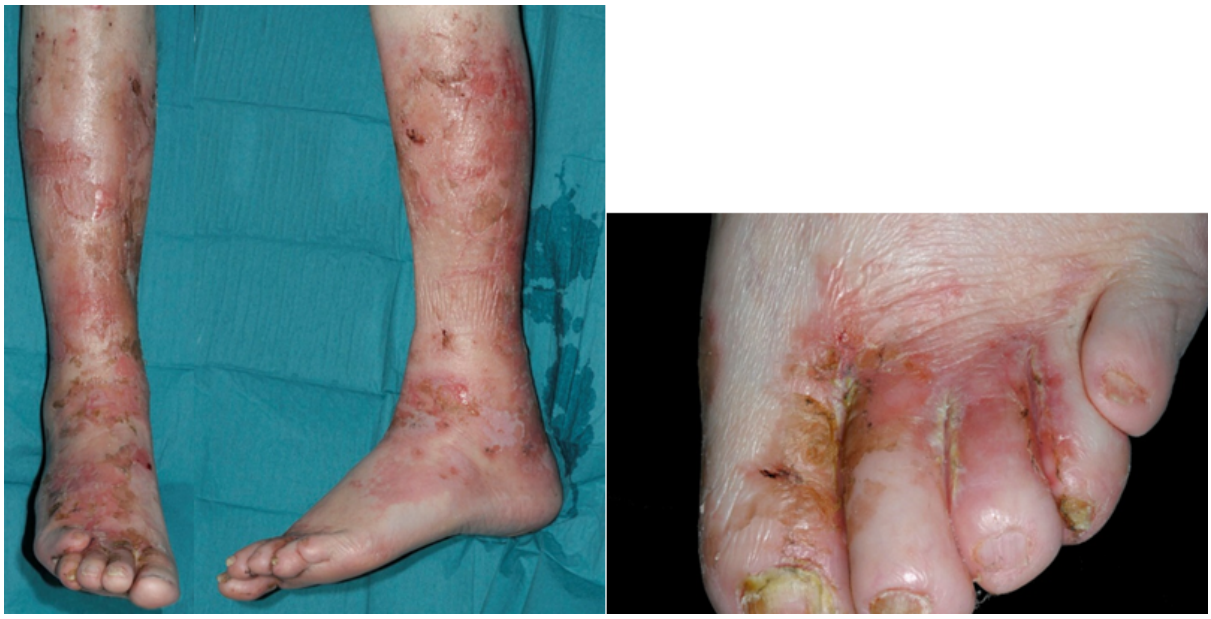

Figure 2. Necrolytic migratory erythema in a glucagonoma patient

Almost invariably, the NME resolves after successful removal of a glucagon-producing tumor, even if the rash has been present for several years (9). In addition, in patients who do not undergo curative resection but are treated with somatostatin analogs, everolimus, or peptide receptor radionuclide therapy (PRRT), the dermatitis improves (10). Historical reports mention improvement of the NME rash with amino acid repletion as well as administration of carbohydrates but this has not been confirmed in recent series (11).

A typical clinical presentation of glucagonoma is usually when these tumors are over 4-5 cm in size and metastatic dissemination has occurred, particularly in the liver (3). The 10-year survival of a localized (and subsequently surgically resected) glucagonoma is nearly 100%, but decreases to 50% in the case of metastatic disease (2). The clinical incidence of glucagonomas is estimated at 1-2% of pancreatic neuroendocrine neoplasms (panNENs) and about 2 cases per million population (12, 13).

About 10% of glucagonomas are diagnosed in patients with multiple endocrine neoplasia type-1 (MEN-1) (14). Patients with MEN-1 have an increased risk to develop pituitary, parathyroid. and panNENs including glucagonomas. A second, however rare, syndrome associated with hyperglucagonemia is the *Mahvash* syndrome (15). This autosomal recessive hereditary syndrome is caused by a biallelic inactivating mutation of the glucagon receptor gene. Defective glucagon signaling causes hyperglucagonemia and alpha cell hyperplasia which can eventually give rise to panNEN. Since the first reported patient in 2008, a total of 11 patients have been reported in the medical literature and the estimated prevalence is 4 per million population. In patients with *Mahvash* syndrome, hyperglucagonemia does not cause the glucagonoma syndrome, due to a defective glucagon receptor.

Secondary, or metachronous glucagon secretion panNENs which previously were non-secreting, or secreted other peptide hormones can also occur (16, 17).

DIAGNOSIS AND CLINICAL WORK-UP

The diagnosis of the glucagonoma syndrome is based on the combination of elevated plasma glucagon levels and symptoms fitting a glucagonoma as previously described. 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 shunting, other NENs, and familial hyperglucagonemia (18). However, a fasting plasma glucagon >500 pg/ml (reference range, 70–160 pg/ml) is diagnostic for glucagonoma (19).

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. To detect distant metastases, somatostatin receptor imaging should be used as glucagonomas express high numbers of different somatostatin receptor subtypes. The study by Kindmark and colleagues revealed that somatostatin receptor scintigraphy was positive in 97% of glucagonoma patients (20). Currently, positron emission tomography (PET)-CT with gallium-labelled somatostatin analogs (DOTATATE, DOTANOC, DOTATOC) have the highest sensitivity for detecting metastases of grade 1-3 panNENs (21, 22). 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 (23). An overview of the current staging and grading systems is provided in the chapter “Insulinoma”.

TREATMENT OF GLUCAGONOMAS

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 should be performed to resect the glucagonoma. In selected patients with limited liver metastases an extended surgical resection can be considered (24). Preoperative preparation is required including correction of malnutrition and hyperglycemia. Somatostatin analogs should be started to reverse the catabolic state and improve the skin rash. Prophylactic measures to prevent venous thrombosis, including the use of low-molecular weight heparin, should be applied to all patients during the perioperative period.

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 non-functioning panNENs as specific data for glucagonoma is often lacking. The guidelines by ENETS, NANETS, and ESMO describe the selection and sequencing of somatostatin analogues, targeted therapy, ^{177}Lu-DOTATATE and cytotoxic chemotherapy (25-27).

Somatostatin Analogs

Somatostatin analogs are the palliative treatment of choice to control glucagon secretion and tumor growth. In a randomized controlled trial (CLARINET), including grade 1-2 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 (28). Moreover, somatostatin analogs have been reported to decrease the NME (10).

Peptide Receptor Radionuclide Therapy

The expression of somatostatin receptor subtypes provides an opportunity to utilize peptide receptor radionuclide therapy (PRRT) for the treatment of

metastatic glucagonomas. PRRT with ^{177}Lu-DOTATATE has been approved for the treatment of grade 1-2 panNETs based on the NETTER-1 trial for midgut NET (29) combined with prospective Erasmus MC, Rotterdam data for panNET. In general, the response rate for grade 1-2 panNETs is the highest of all NETs (55%), with a median PFS of 30 months and median overall survival (OS) of 71 months (30). Sub-acute toxicity mainly includes nausea, vomiting, and CTCAE grade 3/4 toxicity of hematologic parameters (10%). In 70% of patients with toxicity, the hematologic parameters normalize but 1% of patients treated with PRRT develop acute leukemia, and 2% myelodysplastic syndrome (30). PRRT with ^{177}Lu-DOTATATE for the treatment of metastatic glucagonoma has been described in small case series. The radiological response rate of glucagonomas seems to be comparable with non-functioning grade 1-2 panNETs. Of particular value is the high symptomatic response rate (71%) and the increase in quality of life after treatment with ^{177}Lu-DOTATATE (31).

Everolimus

Treatment with everolimus inhibits mammalian target of rapamycin (mTOR) signaling. In the RADIANT-3 trial, everolimus 10 mg/day increased progression-free survival in grade 1-2 panNETs to 11 months as compared to 4.6 months with placebo. Also, overall survival increased from 37.6 to 44 months (32). In this study 24% of patients had a functioning grade 1-2 panNET. In a post-hoc analysis, everolimus was found to decrease plasma glucagon levels in patients with elevated glucagon (33). However, median plasma glucagon was only 1.5 times the upper limit of normal in these patients suggesting that they did not suffer from the classical glucagonoma syndrome. As 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.

Sunitinib

Sunitinib is currently one of the other options for treatment of grade 1-2 panNENs during treatment with a first generation long acting somatostatin analogs. In the SU011248 trial sunitinib 37.5 mg/day increased progression-free survival to 11.4 months in comparison to 5.5 months with placebo in patients with predominantly grade 1-2 panNETs. Overall survival did increase from 29.1 to 38.6 months. In this trial, 5 patients with a glucagonoma (3%) were included (34). However, radiological and symptomatic efficacy for this subgroup of glucagonoma patients was not reported.

Chemotherapy

In a retrospective series from 2007, treatment of 18 patients with a glucagonoma with streptozotocin (STZ) and 5-fluorouracil (5-FU) resulted in an objective response in 50% of patients (20). Chemotherapy with capecitabine and temozolomide is also effective for the treatment of panNET but no specific data for glucagonoma are available (35, 36).

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. Liver metastases can be resected or treated by bland embolization, radioembolization (SIRT), radiofrequency ablation (RFA), microwave and cryoablation, high-intensity focused ultrasound (HIFU), laser, brachytherapy and irreversible electroporation (IRE) depending on local availability (37).

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