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Review

Glucagonoma

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SUMMARY

Glucagonomas are rare endocrine pancreatic tumors manifested by a well-known clinical syndrome. They may occur either sporadically (87%) or as part of multiple endocrine neoplasia syndrome type 1 (MEN 1) (13%). Tumors, with some rare exceptions, are located exclusively in the pancreas (mainly in the tail, that is at the distribution site of the glucagon-secreting A cells) and secrete excessive amounts of glucagon. They are usually large and solitary. In the majority of the reported cases, glucagonomas are malignant and there is a close correlation between tumor size and malignancy. Liver and lymph nodes are common sites of metastases. Both sexes appear to be affected with equal frequency and the average age at the time of diagnosis is 52.5 years. Clinical manifestations include a skin rash, termed necrolytic migratory erythema, (although characteristic, it is not pathognomonic, since similar lesions have been reported in other situations), glossitis/stomatitis/chelitis, weight loss or cachexia often associated with anorexia and thromboembolic problems. Diarrhea, ophthalmic, neurologic or psychiatric manifestations have also been reported. Hyperglycagonemia, diabetes or glucose intolerance (73.3%), hypoaminoacidemia (41.2%), normochromic normocytic anemia (33-85%) and often elevated sedimentation rate are the major biochemical findings. Elevated levels of other polypeptide hormones have also been reported. Chronic hyperglycagonemia that produces hypoaminoacidemia, perhaps in combination with other non-known tumor products or metabolic disturbances are responsible for the skin eruption. The diagnosis may be delayed for many years and will be advocated in patients with unexplained chronic dermatitis, particularly if associated with buccomucosal inflammation, diabetes or glucose intolerance, weight loss or unexplained thomboembolic episodes. The existence of hyperglucagonemia (>1000 mg/ml) may establish the diagnosis. The localization of tumor or metastases may be made by imaging methods (mainly be endoscopic U/S and angiography) or by surgical exploration. Surgery (enucleation of the tumor, distal pancreatectomy, major pancreatic resection, debulking of unresectable or metastatic disease) is the treatment of choice. Embolization of hepatic artery, chemotherapy or somatostatin analogues (octerotide or lanreotide) are the alternative solutions. The prognosis, despite the malignant nature of the tumor, is relatively good, due to its slow growth. The 10-year survival rate is 51.6% in patients with metastases and 64.3% in those without metastases.

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Terminology. The term "glucagonoma" is used for description of endocrine pancreatic tumors that secrete usually excessive amounts of glucagon. These tumors may or may not be associated with characteristic clinical and biochemical findings, such as necrolytic migratory erythema, hypoaminoacidemia and diabetes or glucose intolerance. Different other terms, such as "glucagonoma syndrome",[1] "hyperglycemic cutaneous syndrome",[2] "diabetes-dermatitis syndrome",[3] and "catabolic syndrome"[1,4] are also in use.

Historical view. The first well-documented case of glucagonoma was published in 1966 by McGavran et al.[5] Neanmoins, Becker et al,[6] in 1942, described a case in a 45-year-old woman with loss of weight, diabetes mellitus, anemia, stomatitis and [2]vesiculopapular rash, characterized as "unique", that was associated with islet-cell carcinoma of the pancreas. The authors were the first to note a correlation between skin lesions and islet-cell tumors.

Between 1942 and 1966 several other authors[7-17] noted the association of islet-cell tumors with clinical or biochemical findings (skin lesions, diabetes mellitus, presence of glucagon in tumor extracts etc.) that would be compatible with "glucagonoma" as it is defined today. After the first well-documented description of McGavran et al,[5] Wilkinson,[18,19] an English dermatologist, describes the clinical features of the skin lesions and introduces the term "necrolytic migratory erythema" because of the migratory character of the skin eruption. The first full description of the many clinical features which comprose the glucagonoma syndrome was made by Mallinson et al.[1]

EPIDEMIOLOGY

Incidence. Glucagonomas are rare tumors (third in frequency, after insulinomas and gastrinomas among functional pancreatic endocrine tumors) with an estimated incidence of only 1 in 20 million[20] or 0.05-1 new cases/million/year.[21] Until 1998, 407 cases had been reported worldwide.[22] These tumors may occur either sporadically (87%) or as part of multiple endocrine neoplasia syndrome type 1 (MEN 1) (13%).[22-24] The patients of this latter group initially present with other features, such as hyperparathyroidism, and the age at diagnosis is usually below 40 years[20].

Sex. Both sexes appear to be affected with equal frequency.[25] In a recent analysis of 407 cases, a male:female ratio of 0.8 was noted.[22]

Age. The youngest reported patient was 11 years and the oldest 88 years, with an average age of 52.5 years.[22] Generally, the syndrome is rare among children and this may be due to the very slow growth of these tumors.[25] Glucagonomas become symptomatic after they have grown large (which may require many years) with a high level of glucagon production.[25] The age at first diagnosis appears to be decreasing in more recent series, owing to the increasing awareness among physicians and the greater sensitivity of newer diagnostic methods. When asymptomatic, the tumors are detected at a younger age only in the case of patients with known MEN 1 who undergo screening.[20]

PATHOLOGY

Tumor location. Nearly all glucagonomas (97.3%) are located in the pancreas[22,25] (53.7% in the tail, 32.2% in the body and 21.9% in the head, while in 1.7% the location is not specified[22] or is unknown[26]). In few patients was the location extrapancreatic, such as in kidney,[27,28] duodenum,[29] lung,[30] accessory pancreatic tissue,[31] jejunal adenocarcinoma,[32] liver[33] and hepatoduodenal ligament.[34] This tumor's location has important implications when planning surgical resection. Tumors in the head of the pancreas may require a Whipple's procedure which is associated with high morbidity and mortality.[20]

Size/Malignancy/Metastases. Clinically active tumors are usually larger in size than other functional endocrine tumors, with a mean diameter of 5 cm.[25] It appears that there is a close correlation between tumors size and malignancy.[22,25] Tumors below 2 cm in diameter are associated with a very low (8.75%) incidence of malignancy (table I)[22]. In patients with MEN 1 the tumors have a lower rate of malignancy (24.5% vs 66.1%)[22]. The majority of reported cases have been solitary tumors[25]. In patients with MEN 1 the tumors exhibit a lower rate of multiplicity (4.8% vs 58.5%).[22]

Around 90% of patients with glucagonoma have metastases at the time of diagnosis.[20] The most common site for distal metastases is the liver (80%), followed by lymph nodes (37.8%), bone (8.1%), mesentery/omentum/peritoneum (4.8%), lung (2.1%) and adrenals (1.4%).[22] Hepatic metastases are usually multiple in 2/3 of cases and involve both lobes of the liver. Of the single hepatic metastases 75% occur in the right lobe.[20]

Tumor histology. Histologically, glucagonomas show no remarkable characteristics and feature general endocrine morphology.[35] Mitotic figures and nuclear atypia are rare.[36] Immunostaining is positive for glucagon-containing granules, indicative of their alpha cell origin. Many glucagonomas, however, are pleomorphic[36,37] with cells containing granules that stain for other peptides, most frequently pancreatic polypeptide.[36,38] Electron microscopy reveals a variable number of secretory granules. Benign tumors are usually fully granulated, whereas malignant cells have fewer granules.[35,39]

Histology of skin lesions. The histologic appearance of an early lesion taken from the edge of the rash is characterized by superficial spongiosis and necrosis in the upper layers of the stratum Malpighi and subcorneal blis-

Table I[22]

Tumor size	Malignancy
<2cm	8.7%
2.1-5cm	31.2%
>5cm	66.7%

ter formation.[25] Generally skin biopsies can show a variety of findings: epidermal necrosis, subcorneal pustules (isolated or associated with necrosis of the epidermis), confluent parakeratosis, epidermal hyperplasia, marked papillary dermal angioplasia, and suppurative folliculitis. No single histologic feature is specific for the disease, but a combination of the features is probably diagnostic. Therefore, multiple skin biopsies are recommended when this diagnosis is suspected.[40]

CLINICAL FEATURES

Skin lesions. The unusual skin rash, termed as "*necrolytic migratory erythema*",[19] is the most characteristic clinical finding and is almost always antedated by the onset of diabetes. This skin eruption is not pathognomonic, since similar lesions have been reported in other situations, such as acrodermatitis enteropathica due to zinc deficiency,[41,42] pemphigus (foliaceus, chronic benign familial)[16,43] and toxic epidermal necrolysis.[44] The rash has also been reported in a few patients without pancreatic tumors (possible pseudoglucagonoma syndrome ?),[45-48] such as coeliac diase,[1,49] liver cirrhosis,[45,50,51] rectal adenocarcinoma,[52] squamous cell carcinoma of the hypopharynx[53], or after exogenous administration of glucagons.[54,55] Erythema multiforme, secondary to intravenous glucagon administration, has also been reported.[56]

The rash, in the classical descriptions,[1,3,19] usually starts at various sites, is often wide-spread and most severe on the groins, lower abdomen, perineum and between thights and buttocks. Initially the lesions begin as erythematous and scully. Later they become raised with superficial central blistering, and confluent, and rupture early to leave crusts or, in areas exposed to friction (as the groins and feet) a weeping surface. The lesions tend to heal in the center while the margin spreads with a red, crusting, well defined edge and an annular or figurate outline. Healing results in hyperpigmentation and induration of the skin. The whole sequence usually takes 7-14 days to complete and among the characteristics of the skin rash is the coexistence of old and new lesions separated by normal skin. Trauma from shoes, earrings, or sticky tape, frequently plays a role in the location and intensity of the lesions and produces angular or linear lesions in apparently unaffected skin.[25] Superinfections caused by bacteria or fungi are common.[57]

Glossitis/Stomatitis/Chelitis. All mucous membranes may be affected by the rash, leading to angular chelitis, glossitis and stomatitis with an incidence of 33%.[58,59] Chronic vulvovaginitis is reported in 12% of patients.[39] Abdormalities of hair growth occur in some patients.[39]

Weight loss. Marked weight loss or cachexia, often associated with anorexia, is a cardinal sign of glucagonoma, occurring in 62.5% of symptomatic patients (14.9% in those with local disease) with increased incidence in patients with metastases.[20,22] The weight loss may be profound and is often associated with large tumors and high plasma glucagon levels and is primarily caused by the catabolic effects of chronic hyperglucagonemia and secondarily to other less specific tumor effects.[25]

Thromboembolic problems. Deep venous thrombosis and pulmonary embolism appear to be more common in patients with glucagonomas than in patients with other endocrine pancreatic tumors,[25] occurring in around 11% of all patients and may be life threatening.[20] Because they have been the cause of death in some patients, they should be searched for carefully and, if found, treated aggressively. The reason for patients' increased tendency to develop thromboembolic phenomena is not known.[25]

Other. Diarrhea occurs in about 15-25% of patients,[20,39] but the cause is not known. Other non-specific manifestations such as dementia, ataxia, optic atrophy, central scotomata, retrobulbar neuritis, epigastric pain, lower limb weakness, psychiatric disturbances (depression or paranoic delusions),[20,60-62] or morbid obesity[63] have also been reported.

Because of potentially fatal secondary endocrine syndromes (e.g. gastrinomas[20,64-66] or vipomas[67]) which may develop even many years after the initial diagnosis, patients should be advised to report any new symptoms promptly. It is recommended that fasting gut hormone measurements are made each year, indefinitely.[20]

BIOCHEMICAL FINDINGS

Hyperglucagonemia. Diagnostic plasma glucagon concentrations have not been precisely established. In practice, levels in excess of 1000 pg/ml can be considered biochemical evidence for glucagonoma. Moderate hyperglucagonemia (less than 500 pg/ml) has been reported in other conditions, such as stress (trauma,[68] burns,[68-70] infections,[57] surgical procedures), diabetic ketoacidosis,[71] chronic renal[72] and hepatic failure, particularly in portocaval systemic shunt,[73-75] (probably as a consequence of hypersecretion by negative feedback mechanism[76]), glucocorticoid treatment or Cushing's syndrome,[77,78] exercise,[21] acute pancreatitis, starvation[21] or

other situations.[79] In addition, in some asymptomatic subjects very high levels of plasma glucagon (500-1200 pg/ml)[80] have been reported, either sporadically or familially.[22,58,80-82] Their glucagon appears to consist predominantly of a high molecular weight species, that is not bioactive and reacts with glucagon radioimmunoassay. They can be identified by fractionation of their immunoreactive plasma glucagons.[25]

Although pancreatic endocrine tumors constitute an integral component of the multiple endocrine neoplasia type 1, the association of glucagonoma syndrome with MEN 1 is relatively rare.[23,24,83] It is reported that MEN 1 patients had significantly higher mean basal levels of plasma glucagon even in the absence of pancreatic endocrine tumors.[84] Accordingly, the findings of only modest elevations of plasma glucagon levels is not useful for the early detection of glucagonoma in MEN 1.[85]

Hypoaminoacidemia. Amino acid deficiency and severe skin rash have been reported in patients with glucagonoma[1,86,87] and have also been reported after glucagon administration.[54,88] Hypoaminoacidemia is present in 41.2% of symptomatic patients and only in 4.6% of patients with local disease.[22] Also plasma and tissue zinc concentrations are often low. Its role in the skin rash is discussed below. Glucogenic amino acids are more affected than branched-chain amino acids,[25] and there is frequently a good correlation between plasma glucagon levels and amino acid concentrations.[25]

Anemia. Normochromic normocytic anemia occurs in 33-85%,[20,59] with normal serum iron, B12 and folate levels, probably due to direct bone marrow suppression by glucagons.[20,39]

Diabetes/Glucose intolerance. The incidence of diabetes or glucose intolerance is 73.3% in symptomatic patients and 35% in those with local disease.[22] The diabetes may require insulin therapy.[20] The pathophysiologic mechanism is not precisely known; glucagon and insulin appear to play a role but plasma glucagon levels do not correlate well with serum glucose levels.[25] The development of diabetic ketoacidosis is an unusual complication of a glucagonoma, with only four reported cases in the literature.[90]

Elevated ESR. Elevated erythrocyte sedimentation rate has been reported.[41]

Other. Glucagonomas, as other islet-cell tumors, may secrete multiple hormones,[59,91-96] such as insulin,[5,97-100] pancreatic polypeptide,[1,38,90] ACTH,[101-104] parathyroid hormone or substances with parathyroid hormone-like activity,[97,105] gastrin,[92,97,101,102,104] serotonin,[90,92,98] VIP,[98] MSH,[104] somatostatin.[90,106]

PATHOPHYSIOLOGY

The cause of the skin rash still remains unclear.[22,25] A direct effect of glucagon on the skin,[44] prostaglandin release,[64] amino acid[1,107] or essential fatty acid[107] or zinc[108,109] deficiency (because of similarity to acrodermatitis enteropathica) have been proposed as the underlying cause.[110-113] In some patients the skin rash can be reversed or partially relieved by parenteral nutrition.[114,115] The data for the role of hyperglucagonemia and hypoaminoacidemia in the pathogenetic mechanisns of the skin rash remains controversial since the acute normalization of the hyperglucagonemia with somatostatin administration can improve the skin lesions while plasma amino acids are still decreased. On the other hand, normalization of blood amino acid levels through intravenous amino acid infusion[115] has been shown to correct the dermatitis irrespective of glucagon concentrations.[114] It is likely that chronic hyperglucagonemia, perhaps in combination with other unknown tumor products or metabolic disturbances, is responsible for the skin lesions.[116-118]

DIAGNOSIS

There may be considerable delay from the time of onset of symptoms to the diagnosis, sometimes many years. This may be due to the failure to recognize common features such as diabetes, weight loss, or thrombosis as a manifestation of an uncommon syndrome, or to recognize the characteristic rash.[20] In addition, because of an apparent responsiveness to different empirical medications, the diagnosis of necrolytic migratory erythema is not considered, and the diagnosis of pancreatic carcinoma may be delayed for a long time.[119]

The diagnosis may be suspected in patients with an unexplained chronic dermatitis, particularly if associated with buccomucosal inflammation, diabetes or glucose intolerance, or unexplained thromboembolic episodes, or increased sedimentation rate. Thromboembolic disease with other clinical features, but without migratory necrolytic erythema has also been reported.[120] Establishment of the diagnosis requires demonstration of increased plasma glucagon levels, hypoaminoacidemia, localization of the tumor by imaging methods (Table II), and immunohistochemical assay of the tumor.[121] Glucagonomas, like other neuroendocrine tumors, express somatostatin receptors in more than 80% of cases. Unfortunately, because of the rarity of these tumors, the sensitivity and specificity of octreotide imaging have not been

Table II[22]

Imaging methods	%
Endoscopic U/S	88.9
Angiography	83.2
Computed tomography	82.8
MRI tomography	71.4
ERCP	65.2
U/S	64.5

established. Nonetheless, there have been limited reports in the literature supporting the use of octreotide for glucagonoma imaging and this may be most beneficial as an adjuvant to conventional imaging for tumor staging and therapeutic decision making[149,151]. Although the secretory response of plasma glucagon has been investigated in patients with suspected glucagonoma, the diagnostic value of provocation tests is unproven.[13,21,122,123] In doubtful cases, serial glucagon measurements over several hours can be helpful.[25]

The differential diagnosis of the skin lesions should be made from pemphigus, pellagra, acrodermatitis enteropathica, subcorneal pustular dermatosis, psoriasis vulgaris, eczema, toxic epidermal necrolysis, candidiasis, dermatophytic infection and many others.[124,125]

TREATMENT

Actual treatment of glucagonoma includes surgery, chemotherapy, or octreotide for control of the symptoms. Using a combination of therapies, the majority of patients (54%) with metastatic disease remain symptom free for many years.[20,126,127]

Initial treatment can be directed toward restoration of nutritional status and control of the symptoms, and hyperglycemia. Some patients are treated with zinc sulfate supplements or topical zinc ointment for the skin eruption.[20,41] Blood transfusions and parenteral nutrition with restoration of plasma amino acid levels to normal have an excellent effect in healing skin lesions.[21,114] Chronic warfarin or heparin therapy is commonly needed to prevent thromboembolic events.[39]

Surgical. This is the treatment of choice and the only chance for cure.[20-39] If the tumor is small and solitary, enucleation is the best. Large or multicentric tumors require pancreatic resection. For tumors located in the body and tail, distal pancreatectomy is frequently possible. In most series reported to date, glucagonomas had already metastasized at diagnosis, which means that curative surgery is possible to perform in less than half of the patients.[128] Surgical treatment typically entails major pancreatic resection or surgical debulking of unresectable or metastatic disease.[42,129] Complete resection results in rapid disappearance of the necrolytic migratory eryrhema, diabetes mellitus, weight loss, and diarrhea.[42,130] Despite its predominantly malignant nature, prolonged symptom-free survival can be achieved using a targeted combination of surgery, hepatic artery embolization and somatostatin analogues.[20] Aggressive cytoreductive surgery results in prolonged remission.[131]

Embolization. It is used in hepatic metastases with rapid amelioration of the syndrome's manifestations,[101,132] but in 50% of cases symptoms recur within 6 months. Portal vein occlusion is an absolute contraindication. Other contraindications include prolonged prothrombin time, replacement of more than 50% of the liver parenchyma with tumor, marked reduction of liver function, intercurrent infections and end-stage disease[20]. Mild side-effects are common, but serious complications are rare.[20]

Chemotherapy. Chemotherapy seems of little benefit, and is often only given in advanced disease.[20] A variety of chemotherapeutic agents, such as streptozotocin, dacarbazine, doxorubicin, 5-fluorouracile, chlorozotocin (similar to streptozotocin but less nephrotoxic), lomustine and others have been used in the treatment of glucagonomas and other endocrine tumors, alone or as part of multi-drug combinations.[62,132-142] Streptozotocin and 5-fluorouracile or doxorubirin have been used more specifically in the treatment of glucagonomas, mainly in patients in whom other treatments had failed and who were, therefore, at a more advanced stage of disease.[20] Streptozotocin is associated with considerable toxicity, especially nephrotoxicity.[20,134]

Somatostatin analogues. Octreotide, or a newly developed long-acting somatostatin analogue (lanreotide[143]), is a valuable treatment for rapid improvement of skin lesions in a few days, increases body weight, suppresses glucagon secretion (but not always[144]), and controls diarrhea, and abdominal cramping, although it does not prevent tumor growth.[35,145,146] It is also ineffective in controlling diabetes mellitus due to the reduction in plasma insulin caused by the drug.[41,146] Progressive dose increases are usually needed long term to maintain the same clinical response.[20]

Interferons. Interferon alone or in combination with octreotide can have antiproliferative efficacy in some patients with endocrine pancreatic tumors.[132,147,148] Generally, experience is limited because of the rarity of glu-

cagonomas and the small number of reported cases.

PROGNOSIS

The 10-year survival rate is 51.6% in patients with metastases and 64.3% in those without metastases.[22] In general, glucagonomas, despite the high rate of malignancy and the presence of metastases at the time of diagnosis follow a very slow natural course and with the application of the various therapeutic modalities currently available, patients can be expected to survive for many years.

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