Glucagonoma: From skin lesions to the neuroendocrine component (Review)

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Abstract. Glucagonoma is a hormonally active rare pancreatic neuroendocrine tumour causing an excess of glucagon. This is a narrative review based on a multidisciplinary approach of the tumour. Typically associated dermatosis is necrolytic migratory erythema (NME) which is most frequently seen at disease onset. Insulin-dependent diabetes mellitus, depression, diarrhoea, deep vein thrombosis are also identified, as parts of so-called 'D' syndrome. Early diagnosis is life saving due to potential aggressive profile and high risk of liver metastasis. NME as paraneoplastic syndrome may be present for months and even years until adequate recognition and therapy; it is remitted after successful pancreatic surgery. Thus the level of practitioners' awareness is essential. If surgery is not curative, debulking techniques may improve the clinical aspects and even the outcome in association with other procedures such as embolization of hepatic metastasis; ablation of radiofrequency type; medical therapy including chemotherapy, targeted therapy with mTOR inhibitors such as everolimus, PRRT (peptide receptor radiotherapy), and somatostatin analogues (including combinations of medical treatments). Increased awareness of the condition involves multidisciplinary practitioners.

Contents

1. Introduction

Glucagonoma is a hormonally active rare neuroendocrine tumour causing an excess of glucagon (1-3). The clinical presentation is heterogeneous and it is defined as glucagonoma syndrome (GS) (1-3). The glucagon excess is provided by a neoplasia at the level of α pancreatic cells (so called 'functional' pancreatic tumours) with a usual slow rate of growth (1-3). The typical skin lesion (the dermatosis) induced by a glucagonoma is a rash called necrolytic migratory erythema (NME) which is most frequently seen at disease onset (1-3). Insulin-dependent diabetes mellitus, depression, diarrhoea, deep vein thrombosis are also identified, as parts of so-called 'D' syndrome (4-6). Severe intestinal transit damage causes malnutrition in association with glucose metabolism anomalies (4-6). Typical glucagonoma triad includes NME, diabetes and weight loss (4-6). Also infections such as stomatitis has been reported in some subjects (7,8).

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Abbreviations: GS, glucagonoma syndrome; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; NME, necrolytic migratory erythema; PET, positronic emission tomography; pNET, pancreatic neuroendocrine tumours; PRRT, peptide receptor radiotherapy

Key words: necrolytic migratory erythema, rush, glucagonoma, neuroendocrine, somatostatin, glucagon

Early diagnosis is life saving due to the potentially aggressive profile and high risk of liver metastasis (6-8). NME as paraneoplasic syndrome may be present for months and even years until adequate recognition and therapy, and it is remitted after successful pancreatic surgery (9,10). Thus, the level of practitioners' awareness is crucial (10).

2. Method

Our purpose is to present a narrative review regarding the complex medical panel in glucagonoma. The research is mainly based on recent articles published in PubMed indexed journals. The data are introduced following practical points though a multidisciplinary approach. The inclusion criteria were met by 60 articles.

3. Glucagon as hormone

Glucagon, a hormone of 29 amino acids, is derived from pro-glucagon (a peptide) and it is secreted by α cells of the pancreas (11-13). It regulates the metabolism of amino acids, and it increases glucose level due to stimulation of gluconeogenesis and glycogenolysis and long term exposure to high blood glucagon may induce diabetes mellitus through insulin resistance (it represents the major contributor to insulin resistance) (11-13). Glucagon has an antagonist action of liver insulin inducing gluconeogenesis and it acts through enhancing hepatic glucose output, and skeletal muscle output of amino acids as fuel for glucose synthesis and also stimulating fatty acid oxidation as energy source for the process (12). Glucagon and associated insulin resistance is linked not only to diabetes but also to the entire area of metabolic complications such as obesity and cardiovascular morbidities since it is connected with energy expenditure and body weight control (14-16). Hyperglucagonemia is caused by glucagonoma, post-operatory status after gastric bypass, and non-alcoholic fatty liver disease (11). Glucagon release is inhibited by incretins such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) which stimulate insulin and is the basis of type 2 diabetes mellitus medication, also with a potential use in obesity (17,18). These are gastrointestinal hormones that have emerged as pharmacological applications (17,18). GLP-1 also stimulates gastric emptying, reduces food intake, stimulates dieresis and displays cardio-protection (17,18). Gut-derivate hormones as well as pancreatic hormones such as glucagon or insulin also communicate with bone regulator pathways, including local skeleton nets and bone turnover modulators such as collagen-associated markers or 5-hydroxytriptamine (16,19).

4. Glucagon producing tumour

Glucagonoma is one of the pancreatic neuroendocrine tumours (pNET) which include heterogeneous functional neoplasia such as glucagonoma, somatostatinoma, insulinoma, etc. (functional pNET represents up to 40% of all pNET) in association with non-functional pNET (pNET comprises 1-2% of all pancreatic neoplasia) (20-22). Neoplasia of pNET type had an increasing incidence of 4,8/100,000 persons in 2012 (20). Gene anomalies of MUTYH and mTOR have been reported in pNET (20). The panel of investigations goes beyond clinical presentation which is variable depending of secreted hormone to blood biomarkers such as chromogranin A or neuron specific enolase in addition to histological confirmation according to latest WHO criteria of 2017 (immunohistochemistry is mandatory for an adequate grading) (20,23). Imaging techniques such as computed tomography, magnetic resonance imagery, positronic emission tomography (PET) scan and endoscopic ultrasound guided fine needle aspiration may identify the tumour (20,23).

The surgical approach involves pancreatectomy (potentially associated with liver metastasis resection, splenectomy, local lymphadenectomy or cholecystectomy) (24-26). Surgery of the tumour represents the only curative method at present while medical therapy is adjuvant/palliative or pre-operatory to release the complications of hormonal excess (20,24-26). The surgical approach is based on the tumour stage and location (24-26). The skin lesions as well as metabolic complications may be completely remitted after successful surgery (20,24-26). If surgery is not curative, debulking techniques may however improve the clinical aspects and even the outcome in association with other procedures such as embolization of hepatic metastasis; ablation of radiofrequency type; medical therapy including chemotherapy, targeted therapy with mTOR inhibitors such as everolimus, peptide receptor radiotherapy (PRRT), and somatostatin analogues (including combinations of medical treatments) (20,24-26).

5. Glucagonoma-associated skin lesions

A study published in 2018 on 623 cases of glucagonoma revealed a mean age of 52.4 years and men to women ratio of 0.79 (27). Their presentation included most frequently NME of 82%, followed by diabetes mellitus 68%, weight loss 60%, anaemia in almost half of the subjects, and glositis/stomatitis/cheilitis of 41% (27). Almost two thirds of the glucagonomas were located at pancreas tail while a mean tumour diameter was 5 cm, and almost half of the patients had liver metastasis at first diagnosis (especially in older persons) (27). The time from GS to glucagonoma recognition was 31.4 months (27).

NME represents a challenging condition of multiple differential diagnosis and it represents the central element of GS (28-30). Prompt recognition is imperative in order to adequately treat the pancreatic neoplasia (28-30). It appears simlar to annular migrating lesions such as papules or plaques in association with necrosis which is typically at superficial level or bullae or crusted erosions (28-30). Very often the rash has a centrifugal spreading (28-30). The lesions are typically found at extremities, face, and intertriginous area (28-30). Biopsy might provide an adequate diagnosis (28-30). Histological components consists in dyskeratosis (early stages) and psoriasis-like hyperplasia and necrosis in advanced stages (28-30).

Ochi *et al* (31) described the erythema as a 'visual surrogate marker' for glucagon producing pNET. In addition to the rash but less frequent papules associated with pruritus or follicular pustules are found (32). Also, an atypical aspect is psoriasiform skin lesion (33).

Despite its rarity, prompt dermatological diagnosis of NME is the first step of life saving multidisciplinary intervention (34,35).

6. The neuroendocrine component approach

As part of functional pNETs, glucagonoma has a clear neuroendocrine secretion with metabolic and skin consequences (36,37). The lethal potential comes from aggressive profile as a poorly differentiated carcinoma with rapid local and liver spreading or due to dramatic weight loss, glucose metabolism disturbances, and associated infections (36,37). The blood glucagon assay shows a very high value in addition to increased neuroendocrine markers such as neuron specific enolase, synaptophysin, chromogranin A or 5-hydroxytriptamine (38). Immunohistochemistry is positive for neuroendocrine stains as synaptophysin, chromogranin A and, glucagon (39). The Ki67 index of proliferation is a typical prognostic marker in neuroendocrine tumours (40). Somatostatin analogues as octreotide or lanreotide may control tumour growth and diarrhoea or partially/completely the rash or other skin lesions through their actions on type 2 and type 5 somatostatin receptors (39). Cardiac impairment due to tumour-related hyperglucagonemia (which is exceptionally found) might be resistant to this medication (41). The control of symptoms is usually necessary until surgery is feasible (42). While secretor neuroendocrine component is targeted by somatostatin analogues, everolimus, streptozocin, and sunitinib which are also approved for pNET are used for tumour control (43,44). Even in cases where radical intervention is not feasible, analogues of somatostatin are part of the supportive therapy because of total or partial control of GS (45,46). Moreover, their use is also justified in confirmed malignant glucagonomas for NME improvement (45,46).

7. Discussion

Two aspects are important to be further discussed: NME-like lesions and the accidental identification of a glucagonoma as an incidentaloma without typical GS.

NME represents the skin hallmark of a pancreatic tumour activity and very often the first presentation comes from dermatological department (47,48). NME is a complex lesion which is typically associated with glucagonoma and it is part of the paraneoplasic syndrome as seen in other pNETs widely ranging from tumour-related hypercalcemia or hypoglycemia, ectopic Cushing's syndrome to carcinoid syndrome, etc. (49). Lesions that are similar to NME have been reported in non-GS associated liver morbidities (for instance, cirrhosis), malnutrition and inflammatory bowel disease (50,51). The clinical aspects of these conditions involving NME, but not a glucagon producing tumour, have been called 'pseudoglucagonoma syndrome' (50,51). Some cases even reported a similar response to octreotide therapy (52). Another NME-like condition, also very rare, has been described as autoimmune progesterone dermatitis in relation with menses (luteal phase) (53). The presentation varies from urticaria, eczema to erythema of different patterns (53). The differential diagnosis of NME also includes lipase hypersecretion syndrome which is also linked to pancreatic conditions (54). This represents a paraneoplasic syndrome caused by a pancreatic adenocarcinoma with pancreatic enzymes atypically released into the blood and then targeting the subcutaneous areas with local erythema (54).

Another aspect needs to be pointed out in relation to a glucagonoma that is incidentally found until the dermatologic and metabolic complications are positive (55,56). An increased incidence of incidentalomas is registered all over the world and pancreatic masses are one of the most frequent of this kind (56-58). The aspect is described in both neuroendocrine and non-neuroendocrine conditions (59-61). This is mostly related to the increased accessibility to various imaging techniques (56). Incidentaloma underlying glucagonoma has rarely been reported as a synchronous tumour with adenocarcinoma of the pancreas (55). If non-secretor profile is registered, the confirmation of glucagonoma is based on histological report if the subject is referred to surgery or biopsy of liver metastasis (62,63). Pro-glucagon expression is also found in pancreatic glucagonomas while pro-glucagon also is positive in gut tumours that actually produce peptides such as incretins (64).

8. Conclusions

Glucagonoma represents a challenging condition and NME is the main clinical feature and its prompt diagnosis might be life saving. Despite its rarity, the disorder is heterogeneous from metabolic complications to neuroendocrine pattern. Pancreatic surgery offers the best prognostic, but if not feasible, medical therapy including somatostatin analogues might control the glucagon syndrome, including NME. Increased awareness of the condition involves multidisciplinary practitioners.

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Authors' contributions

FS analyzed the data, critically revised the manuscript for its content and was involved in the conception of the study. MC wrote and revised the manuscript, and was involved in the conception of the study. SEA was involved in the literature research, assisted with the acquisition of the information, and was also involved in the conception of the study. AV was responsible for reviewing the manuscript and was involved in the conception of the study. AP was responsible for the literature research and was involved in drafting the manuscript. MCD critically revised the manuscript and was involved in the conception of the study. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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