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Review Article

Glucagonoma syndrome

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Abstract

Glucagonoma syndrome is a rare disease in which necrolytic migratory erythema is often one of the early symptoms. Weight loss and diabetes mellitus are two other characteristics of this syndrome. Necrolytic migratory erythema is typically characterized on skin biopsies by necrolysis of upper epidermis with vacuolated keratinocytes. Persistent hyperglucagonemia results in excessive stimulation of basic metabolic pathway which in turn results in diabetes mellitus at the expense of tissue glycogen stores. Deficiencies of various essential nutrients and vitamin B lead to dermatosis. Due to rarity of glucagonoma, it is quite difficult to diagnose this syndrome at early stages.

Key words

Glucagonoma syndrome, diabetes mellitus, necrolytic migratory erythema.

Introduction

Glucagonoma syndrome is a rare paraneoplastic syndrome consisting of diabetes mellitus, necrolytic migratory erythema (NME), glossitis, weight loss, diarrhea, anemia and hypoalbuminemia.[1]

Incidence

Becker *et al*.[2\] described a patient with typical skin disorder who was to have pancreatic tumor. Later on, McGavran *et al*.[3] documented hyperglucagonemia in association with cutaneous eruptions. The combination of symptoms was termed as the glucagonoma syndrome.

Glucagonoma syndrome has been associated with tumors originating in alpha cells of the pancreas. These tumors demonstrate the typical characteristics of Islet cell tumors; they are usually encapsulated, firm nodules, varying in size from 2 cm up to 25 cm and occur most often in tail of the pancreas.[4]

Age of onset is typically 50 to 60 years and no gender predilection has been observed. Malignancy, defined by presence of metastasis, is reported to be 60-70% but true malignancy rate is as high as 100 percent. Metastasis occurs with most frequency in liver and then in adjacent lymph nodes, bone, adrenals, kidney and lung. (1)

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Pathogenesis

Hyperglycemia linked to glucagonoma is a consequence of the glycogenolytic and gluconeogenic effects of glucagon. Similarly, glucagon excess (or relative glucagon excess) can be observed in diabetes mellitus and its complication, diabetic ketoacidosis.[5]

When glucagon is secreted by a tumor, it becomes independent and is no longer influenced by feedback control mechanisms; the subsequent increase in glucagon concentration in the blood produces characteristic symptoms. Diabetes mellitus occurs in patients with glucagonoma because of the lack of equilibrium between insulin production and glucagon production which occurs when high serum levels of glucagon and normal levels of insulin exist or when insulin production is reduced and a normal glucagon level is present. However, glucagon may not induce hyperglycemia directly unless

the metabolism of glucose by the liver is directly compromised.

Weight loss is due to the action of glucagon on lipid and protein metabolism; increased caloric expenditure, as determined by the protein catabolism; and the consequent increase of gluconeogenesis and urea genesis. This mechanism is probably also responsible for the cases of anemia and hypoaminoacidemia observed in patients with glucagonoma. Thromboembolism, occasionally observed in patients, is attributable to the production of a molecule similar to coagulative factor X from tumor cells.[5,6]

NME is related to the hypoalbuminemia due to glucagon excess; in fact, albumin acts as a carrier for zinc and essential fatty acids. Zinc carries out a fundamental role in the maintenance of cutaneous trophism. The mineral is also responsible for the linoleic acid desaturation and is therefore involved in prostaglandin synthesis, which could determine phlogistic damage to tissues in areas exposed to friction and pressure if it occurs in excess. NME may also occur in areas of cutaneous trauma.[7]

Clinical findings

In glucagonoma syndrome frequency of finding of diabetes mellitus is 56-74%, necrolytic migratory erythema is 70-80%[8] (most common presenting symptom), weight loss and cachexia is 56-91% (marker of metastasis), angular cheilitis and a painful beefy-coloured glossitis is about 33%, diarrhea is 20%, psychiatric disturbances is 14%, venous thrombosis is 10%.[9]

Investigations

For the diagnosis of glucagonoma, investigations include: complete blood count (anemia, normocytic), erythrocyte sedimentation rate (raised ESR), glucose tolerance test (to establish the presence of diabetes mellitus), fasting and random blood glucose levels (hyperglycemia) and serum glucagon level by means of radioimmunoassay (a positive result for glucagonoma exceeds 1000 pg/mL. Reference range is 50-150 pg/mL).[10]

Radiological investigations are helpful in knowing the size and location of the tumor, especially with hepatic metastasis and fundamentally important when deciding on treatment. These investigations include: abdominal ultrasound (detection of tumor mass), CT/MRI/ endoscopic ultrasound (for localization of the tumor), indium-labeled, DTPA (very sensitive test in diagnosis of glucagonoma),[11] selective celiac axis arteriography[12] (gold standard for localization of the tumor and liver metastasis), MIBG scintigraphy (may be helpful in detecting the primary tumor), positron emission tomography scanning (if primary tumor can not be detected on USG,CT or angiography).

Other procedures include; biopsy of skin during an advance stage of the disease (allows a diagnosis of necrolytic migratory erythema).

Based on radiological features, a Tru-Cut biopsy or laparotomy can be performed in order to obtain histological samples.[13]

Treatment

The mainstay of treatment is surgical resection of the primary tumor.[14] Most patients show significant clinical improvement even with incomplete resection of metastasis. Increased level of glucagon secretion can be treated with octereotide, a somatostatin analog.[15]

In advanced metastasis and non-resectable disease, chemotherapeutic agents such as doxorubicin, streptozotocin and 5-fluorouracil

have also been used successfully to selectively damage alpha cells of pancreatic islet. These do not destroy the tumor but help to minimize the progression of the symptoms.[10]

In patients with glucagonoma, providing a supplemental protein supply in order to furnish amino acids is useful. In more severe cases, such supplementation can be administered intravenously. The administration of essential fatty acids (i.e., olive oil), zinc, vitamins, and minerals is also helpful.[16]

Prognosis

Although good prognostic data is still lacking, the over all 5 years survival rate appears to be greater than 50%, and those with localized tumors have complete cure with total resection.[1]

Conclusion

Since glucagonoma is slow growing tumor and good recovery is possible after surgical resection, an early diagnosis is mandatory. Therefore, a high degree of clinical suspicion is essential to diagnose this, otherwise fatal entity, early in its course.

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