

Glucagonoma syndrome: A case report

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Abstract. Necrolytic migratory erythema (NME), diabetes mellitus and glucagon-secreting tumors form the hallmarks of glucagonoma syndrome, and represent the major clinical manifestations of glucagonoma. NME is usually presented as the initial complaint of patients. Due to the rare incidence of glucagonoma, its diagnosis is often delayed, which leads to its progression. Here, we report a case of NME with a typical skin rash, which was misdiagnosed and treated with corticosteroids for two years. Removal of the tumor in the pancreatic body led to the rapid relief of the symptoms. The aim of the present study is to demonstrate the typical characteristics of glucagonoma syndrome to clinicians in order to improve its diagnosis and treatment.

Introduction

Glucagonoma is an uncommon neoplasm of the pancreatic neuroendocrine islet α -cells, whereby the islet cells secrete abundant glucagon (1). The estimated annual incidence of glucagonoma is ~1 case per 20,000,000 individuals (2). Due to the rarity of the disease, mortality rates remain unclear. In a study of 21 glucagonoma patients, Wermers *et al* (3) reported that nine patients succumbed to the disease after a mean duration of 4.91 years following diagnosis (3). Complete tumor resection may cure glucagonoma, with a 10-year survival rate of 64.3% following surgery, however, liver and lymph node metastasis are major risk factors that contribute to tumor-associated mortality (4). For patients with unresectable advanced disease, tumor debulking, chemotherapy or somatostatin may also be considered to reduce the tumor-associated symptoms, however, the survival benefit of such treatments is limited (2,3).

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Glucagonoma induces various manifestations, which are characterized by necrolytic migratory erythema (NME), diabetes mellitus (DM), weight loss, anemia and neuropsychiatric disturbances (1). NME represents the most specific manifestation of glucagonoma syndrome and has therefore provided the most valuable indications for diagnosis in the majority of previous cases (5). Early recognition of NME is likely to lead to a more rapid diagnosis of glucagonoma, thereby allowing surgical resection and achieving a promising therapeutic outcome. This study presents the case of a glucagonoma patient who recovered following spleen-preserving distal pancreatectomy.

Case report

In November 2010, a 50-year-old female presented to The Pancreas Center of Nanjing Medical University (Nanjing, China) with a 2-year history of a pruritic and ulcerating skin rash, which initially appeared at the waist and slowly progressed to the entire body within three months (Fig. 1A). Phacoscotasmus, cheilitis and glossitis were also present (Fig. 1B). The patient also complained of blurred vision and weight loss of 5 kg. The patient was initially diagnosed with pemphigus and treated with prednisone without relief of the skin rash prior to her admission to our clinic. Physical examination revealed that the skin lesions were erythematous macules with erosions, serous exudate and crusting (Fig. 1C). A skin biopsy revealed that the skin layers were arranged normally with mild skin keratosis, basal pigmentation and perivascular infiltration of inflammatory cells in the superficial skin (Fig. 1D). Laboratory tests indicated elevated blood glucose (maximum 18 mmol/l), anemia (87 g/l) and hypoproteinemia (24.6 g/l). Following admission, the patient underwent abdominal computed tomography (CT) scanning, which disclosed a pancreatic body mass with low density (Fig. 2A). Given her history of the skin rash, DM and the pancreatic mass, the patient's blood glucagon concentration was measured, and her fasting glucagon level was noted to be elevated, at 1132.20 pg/ml (normal, 0-80 pg/ml). The patient was first treated with octreotide and intravenous amino acid infusion. After the patient's nutrition was improved, spleen-preserving distal pancreatectomy was performed (Fig. 2B and C). The skin lesions were partially relieved following treatment with octreotide and intravenous amino acid infusion, and gradually recovered following surgery

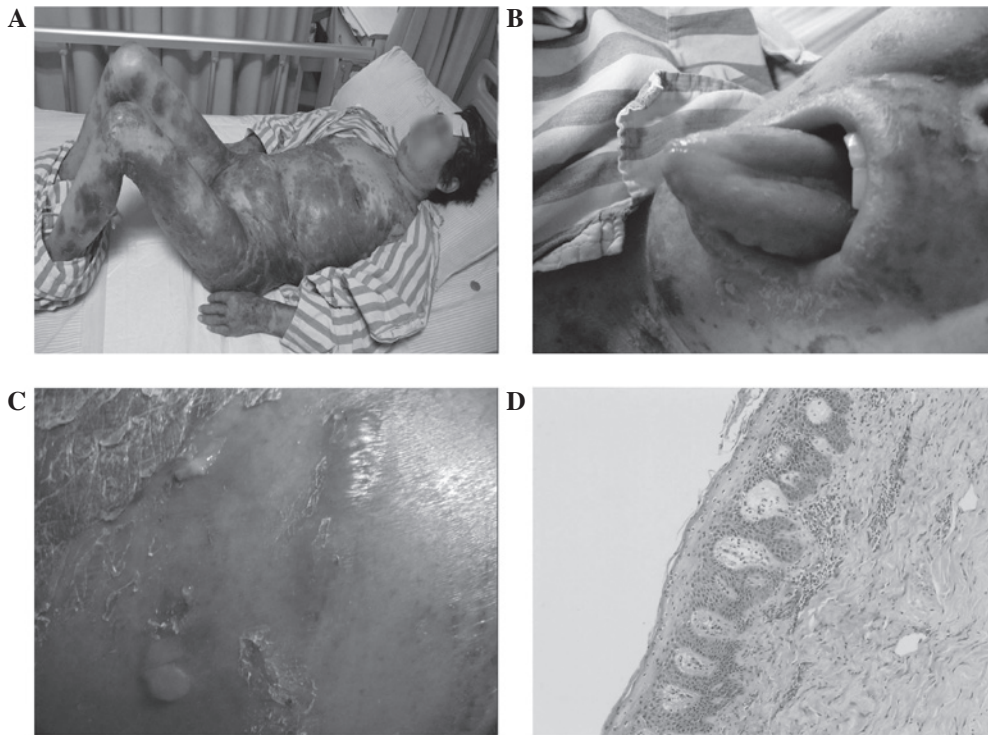


Figure 1. Skin lesions of glucagonoma. (A) Necrolytic migratory erythema. (B) Cheilitis and glossitis. (C) Skin lesions with erosions, serous exudate and crusting. (D) Pathology of the skin biopsy, observed with hematoxylin and eosin staining (magnification, x100).

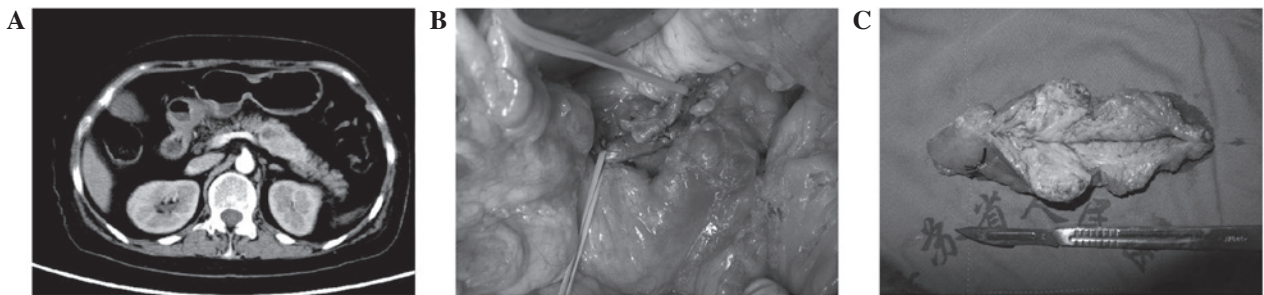


Figure 2. Tumor mass identified by computed tomography (CT) scan and surgical resection. (A) CT scanning indicated the pancreatic body tumor. (B) Laparotomy confirmed the tumor in the pancreatic body. (C) Resected tumor.



Figure 3. Changes in skin lesions following treatment. (A) Skin lesion upon admission. (B) Changes in skin lesions following treatment of octreotide and intravenous amino acid infusion. (C) Relief of skin lesion one week after surgery.

(Fig. 3A-C). Pathological examination confirmed the diagnosis of glucagonoma (Fig. 4A) and immunohistochemical staining revealed the positive staining of chromogranin and

synaptophysin (Fig. 4B and C). Four weeks subsequent to discharge, the skin lesions were completely resolved and blood glucose returned to normal. At 3-year follow-up, the patient

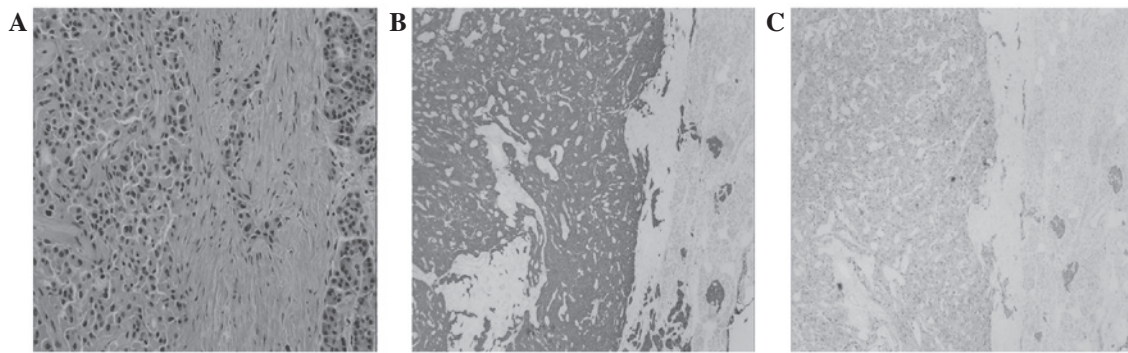


Figure 4. Pathological and immunohistochemistry analysis of glucagonoma. (A) Pathological analysis of tumor by hematoxylin and eosin staining (magnification, x100). (B) Positive staining of synaptophysin and (C) chromogranin by immunohistochemistry (magnification, x40).

remained asymptomatic and no signs of recurrence were detected. The patient provided written informed consent prior to the publication of the study, and the study was approved by the research ethics committee of The First Affiliated Hospital of Nanjing Medical University (Nanjing, China).

Discussion

Glucagonoma, which accounts for 2% of islet cell carcinomas, is a rare neuroendocrine pancreatic tumor with an estimated incidence of one in 20 million (6). Although the diagnostic criteria for glucagonoma has already been established by Stacpoole (7), its rare incidence has hampered prompt diagnosis when the glucagonoma syndrome appears. To date, there are fewer than 300 cases reported in the literature and the largest case cohort included only 21 patients. Delayed diagnosis remains a major issue in the treatment of glucagonoma. The median time between the onset of glucagonoma syndrome and diagnosis is 3-4 years (3,5).

Oversecretion of glucagon by islet α -cells in tumors contributes to the paraneoplastic phenomenon, namely glucagonoma syndrome (5). Glucagon exhibits its physiological functions by increasing the hepatic glucose output and maintaining the blood glucose level (8). Glucagon also exerts a catabolic role by attenuating protein synthesis (9). The elevated glucagon secreted by glucagonoma results in amino acid catabolism and serum glucose elevation, which are considered to be responsible for skin lesions and DM (10). Glucagonoma syndrome consists of a triad comprising glucagon-secreting tumors, DM and NME (11).

NME is considered to be the hallmark of glucagonoma syndrome and is characterized by an annular pattern of erythema with centrally formed fragile vesicles, bullae and crusts (2). It is present in ~65-70% of glucagonoma cases at the point of diagnosis (12). Although a skin biopsy of NME offers limited indications for the pathological diagnosis of glucagonoma, its early recognition may lead to further CT scanning and establish the diagnosis (13). It is worthy to note that celiac disease, malabsorption, cirrhosis, malignancy and pancreatitis may also present NME-like skin lesions, known as pseudoglucagonoma syndrome (14). In the present case, the NME had been misdiagnosed as immune pemphigus and treated with corticosteroids for two years. Although the corticosteroids treatments occasionally relieved the NME,

persistent elevated glucagon inevitably induced its recurrence. In clinical practice, glucagonoma induced by NME should be considered if the skin lesions remain following conventional treatments.

DM is a further clinical hallmark of glucagonoma. Elevated glucagon levels promote the glucose output and antagonize the effect of insulin. Although only 40% of glucagonoma patients presented DM at the onset of symptoms, ~90% went on to develop it (2). The severity of the diabetes remains controversial in the literature, and NME usually occurs prior to the emergence of the diabetes. In the present case, the patient exhibited intermittent glucose elevation one and a half years after the initiation of the skin rash, and the diabetes resulted in the rapid damage of her lens.

Glucagonoma is a slow-growing and relatively low-malignancy tumor. Although numerous glucagonoma patients suffer due to a delayed diagnosis, the majority still benefit from tumor resection. Metastasis represents the main prognostic factor for glucagonoma. Half of all glucagonomas are metastatic at the time of diagnosis (15). Patients without metastasis achieve a 10-year survival rate of almost 100%, compared with 51.6% of patients with metastasis (4). Synchronous resection of liver metastasis or liver transplantation provides a favorable outcome (16,17). Whether patients would benefit from tumor debulking or chemotherapy remains to be elucidated (5,17). For localized glucagonoma, removal of the tumor led to a notable improvement of the glucagonoma syndrome within several days of surgery (18). In the case of malnutrition, total parenteral nutrition with amino acid and caloric supplementation may be used to counteract the catabolic effects of high glucagon and reduce perioperative complications (2). Moreover, somatostatin analog may be useful in relieving glucagonoma syndrome by inhibiting glucagon secretion or counteracting its effect (19).

Although serum glucagon measurement and CT scanning are capable of establishing diagnosis in most cases, the bridge from glucagonoma syndrome to serum glucagon measurement and CT scanning remains a major obstacle to early diagnosis. Few clinicians suspect glucagonoma in its early stages due to its rare incidence. Numerous patients suffer due to the delayed diagnosis and may even miss out on the opportunity of curable resection. For this rare tumor, optimization of the diagnostic procedure based on glucagonoma syndrome is urgently needed.

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