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Malignant glucagonoma: an uncommon cause of new onset diabetes

Glucagonoma maligno como causa infrecuente de diabetes de inicio

To the Editor:

A 44-year-old female patient was initially seen at the endocrinology department for hyperglycemia (random blood glucose level of 580 mg/dL and glycosylated hemoglobin of 10.3%) associated with weight loss, cardinal clinical signs, and severe asthenia. Basal-bolus insulin therapy was started because of the presence of clinical signs of insulinopenia. Two weeks later, the patient started to experience erythematous-desquamative plaque-like lesions in the skin of the upper and lower limbs. The lesions progressively enlarged, were coalescent, and had a patchy distribution. They gradually regressed and cleared at their centres. Other periorificial erythematous and crusty lesions (perinasal, peribuccal, and perianal), severe glossitis, nail dystrophy, progressive alopecia, and blepharitis were also observed. The patient also showed a significantly impaired general condition and mood with progressive weight loss and severe anorexia. She was therefore admitted for a complete work-up.

Initial laboratory tests showed normocytic and normochromic anemia (hemoglobin 10 g/dL), hypoproteinemia with hypoalbuminemia (total protein 5.6 g/dL [normal range (NR): 6.5-8 g/dL] and albumin 2.9 g/dL [NR: 3.5-5.3 g/dL]), and decreased plasma zinc levels (46.9 µg/dL; NR: 70-120 µg/dL). A vulvar tissue biopsy was reported as a skin fragment with a neutrophilic pustule with focal parakeratosis, acanthosis, and a perivascular mixed inflammatory infiltrate suggesting necrolytic migratory erythema (NME). Based on the presence of these lesions together with diabetes mellitus and the systemic picture, glucagon and chromogranin A levels were measured. High glucagon levels were found in two measurements (510 and 655 pg/mL; NR: 59-177 pg/mL), and a high chromogranin A value was also measured (798.8 ng/mL, NR: 19.4-98.1 ng/mL). Glucagonoma was suspected, based on clinical and biochemical evidence, and imaging tests were performed to locate the lesion. In these tests (including helical computed tomography [CT] of the abdomen, cholangio-MRI, and echoendoscopy in chronological order), no tumor lesions were seen in the pancreas or in other locations. In order to locate the lesion, a scan was performed using ^{111}In-DTPA-D-Phe-octreotide (Octreoscan®). This showed a large hyperuptake site of the tracer in the epigastrium midline corresponding to the pancreatic anatomical area, and an additional, less intense accumulation of the radioactive drug in the hepatic border (Fig. 1).

Treatment was started with octreotide 50 µg daily by the subcutaneous route every 12 hours for two weeks, and every 8 hours thereafter. This treatment was well tolerated and induced a clinical improvement in the patient, with the virtual disappearance of skin lesions and a marked decrease in insulin requirements.

Pancreatic glucagonoma was diagnosed, and surgery was performed. Intraoperative examination confirmed the presence of a large lesion involving the body and tail of the pancreas. Laparoscopic corporocaudal pancreatectomy was performed, and the liver surface was examined by intraoperative ultrasound, which showed no lesions. The surgical specimen weighed 46 g and was 8.5 x 4.5 cm in size. A pathological study revealed a disorganized parenchyma with multiple confluent nodules. Necrosis, multiple vascular invasions, and infiltration of peripancreatic soft tissue and resection margins were seen by light microscopy. Immunohistochemical staining was positive for neuroendocrine differentiation markers such as chromogranin and CD56, and for glucagon as a specific hormone marker. The Ki-67 index was 5%-10%. The pathological diagnosis was a multifocal and histologically malignant endocrine tumor consistent with glucagonoma (Fig. 2).

After surgery, octreotide treatment was discontinued, skin and mucosal lesions disappeared completely, and insulin administration was not required. Supplemental tests performed after surgery revealed the disappearance of the hyperuptake site of the tracer located in the epigastrium midline, and no other pathological uptake was seen (Octreoscan®). Abdominal MRI after surgery showed no lesions suggesting metastases or signs of locoregional recurrence.

Chromogranin A levels decreased after surgery, but remained high (577 ng/mL), and glucagon levels returned to normal (71 pg/mL). A genetic study was requested in order to rule out the possibility that the glucagonoma occurred in the setting of multiple endocrine neoplasia type 1 (MEN 1).

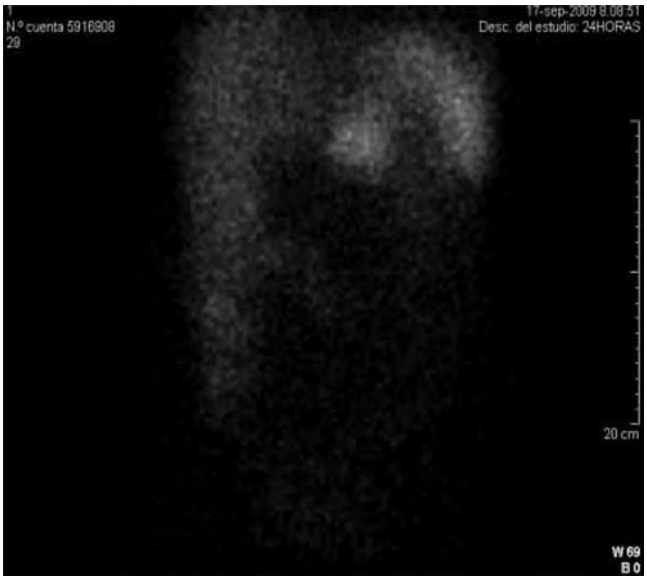

Figure 1 Image of 111In-DTPA-D-Phe-octreotide scan.

A glucagonoma is a rare tumor arising from pancreatic alpha cells. Its incidence is estimated to be approximately 1/20,000,000, and accounts for approximately 7% of all pancreatic neuroendocrine tumors (PNETs)[1]. Glucagonoma occurs more commonly in the fifth decade of life, and no clear sex differences have been found. Most glucagonomas are sporadic, and only 3%-5% of cases are associated with MEN 1[2].

Clinical signs of the disease are usually encompassed in the so-called glucagonoma syndrome, characterized by the presence of NME, diabetes mellitus, weight loss, diarrhea, glossitis, cheilitis, neuropsychiatric symptoms, and thromboembolic events. Initial clinical symptoms are variable, but the most prevalent symptoms in the two largest series that have been reported included the occurrence of skin lesions such as necrolytic migratory erythema (50%-70%), diabetes mellitus (40%-75%), and weight loss (70%). Characteristic biochemical changes in this syndrome also include hyperglucagonemia and hyperglycemia, hypoproteinemia, and normocytic-normochromic anemia[1,2].

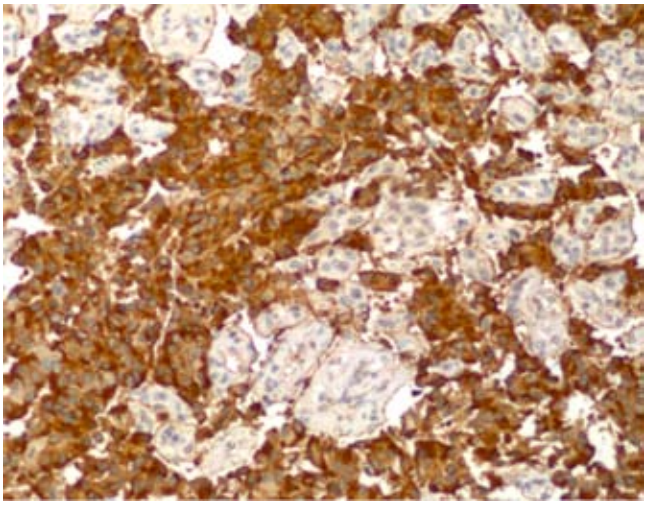

Figure 2 Immunohistochemical stain showing positivity of tumor cells for glucagon.

The development of diabetes mellitus in this condition is mainly related to excess glucagon release and a relative insulin/glucagon concentration ratio favoring the latter, which conditions its glucogenolytic and gluconeogenic effects. Others factors involved in diabetes development include the presence of large pancreatic lesions and hepatic metastases[3]. Diabetes mellitus is diagnosed before glucagonoma in 20%-50% of cases[1,3], and median time from occurrence of diabetes to NME has been reported to be up to four years[3].

NME is the characteristic lesion of glucagonoma, but is not pathognomonic of the condition. Its pathogenesis is not fully elucidated, and hyperglucagonemia, protein catabolism, amino acid and zinc deficiency, and other metabolic abnormalities occurring in the disease have been implicated in its pathophysiology[4]. NME is characterized by the occurrence of erythematous plaques or papules involving the face, perineum, and limbs. This same condition also affects the mucosal membranes causing glossitis, angular cheilitis, stomatitis, and blepharitis. These lesions usually appear in cyclic form and tend to grow and coalesce. Central clearing subsequently occurs, finally leaving a residual hyperpigmentation[5]. Biopsy of these lesions shows superficial necrolysis in epidermis with separation of superficial layers with vacuolated keratinocytes and perivascular infiltration of lymphocytes and histiocytes[2,5].

Glucagonomas are usually large tumors at diagnosis, and liver metastases are found in up to 80% of cases at diagnosis. Other common metastatic sites include regional lymph nodes and bone[1]. Tumors are most commonly located in the tail of the pancreas and are generally solid, circumscribed, and encapsulated. The lesion is usually easy to locate with imaging tests such as CT or magnetic resonance imaging because of its size. In the case here reported, the lesion could only be located using Octreoscan®, despite the fact that a large lesion was found at surgery. In different series, a ^{111}In-octreotide scan was positive in 95%-100% of patients with glucagonoma[1,6]. Echo-endoscopy did not allow for lesion location either. In experienced hands, this procedure has a high sensitivity for the detection of pancreatic lesions regardless of whether they are located in the head, body, or tail of the pancreas, and is able to identify the existence of intrapancreatic lesions, even subcentimetric lesions, in 90% of cases[7].

In the absence of metastasis, primary tumor resection is the curative treatment of choice. As in the reported case, curative resection is usually associated with the resolution of hyperglucagonemia and NME.

Somatostatin analogues have been used before or after surgery. Their use is associated, as in this case, with the regression of NME and decreased insulin requirements[3] and with marked glucagon suppression[2]. Their use as a postoperative treatment for metastatic disease may reduce disease progression[8].

Chemotherapy regimens including interferon alfa, streptozotocin, doxorubicin, and 5-fluorouracil have

achieved inconsistent responses; in some series, biochemical or radiological response was achieved in up to 50% of cases[1], and partial radiological regression in one third of patients[1,3]. In patients with metastatic disease in whom prior chemotherapy has failed, treatment with everolimus has been shown to be effective for disease stabilization[9].

Survival depends on the presence of distant metastases, age, and histological grade[10]. In two of the largest series reported, mean survival of patients with metastatic disease at diagnosis was 4.9 years[3], and 5-year overall survival was 76%[1].

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Partial adrenocorticotropin hormone deficiency associated with multiple sclerosis

Déficit parcial de ACTH asociado a esclerosis múltiple

Isolated secondary adrenal insufficiency is an uncommon condition, except in cases associated with long-term steroid treatment[1]. In adults, it is related to head trauma or lymphocytic hypophysitis of a probable autoimmune origin. We report the case of a patient with a partial deficiency of adrenocorticotropic hormone (ACTH) associated with multiple sclerosis (MS). This association has not been previously reported in the literature. MS is a neurodegenerative disease of considerable clinical heterogeneity caused by a demyelinating inflammatory process of the central nervous system of a probable autoimmune origin. MS is the main cause of disability induced by disease in young adults.

A 39-year-old female patient had a history of two episodes of neurological signs lasting several days, the last of them one year before. Magnetic resonance imaging of the brain and neck revealed multiple white matter lesions. These findings were consistent with a demyelinating disease and met the criteria for MS diagnosis[2]. Treatment was started at that time with corticosteroid bolus injections, and subsequently with copolymer A.

One year later, the patient attended the clinic reporting frequent dizziness, asthenia, and heat intolerance. Laboratory tests made when such signs occurred showed a basal blood glucose level of 48 mg/dL. The patient reported that the symptoms subsided with intake and started before the onset of treatment with copolymer A. She was taking no treatment at the time. Physical examination found her to be 162 cm in height, 57 kg in weight, to have a BMI of 21.7, blood pressure of 90/60 mmHg, and to be otherwise unremarkable.