NECROLYTIC MIGRATORY ERYTHEMA ASSOCIATED WITH GLUCAGONOMA SYNDROME: A CASE REPORT

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Necrolytic migratory erythema is a rare skin condition that consists of migrating areas of erythema with blisters that heal with hyperpigmentation. It usually occurs in patients with an alpha islet cell tumor of the pancreas—or glucagonoma—and when associated with glucose intolerance, anemia, hyperglucagonemia, and weight loss defines the glucagonoma syndrome.

We describe a 52-year-old female patient with necrolytic migratory erythema associated with glucagonoma syndrome who had metastatic disease at presentation and passed away one week after her admission. The autopsy showed a tumor in the body of the pancreas, which was diagnosed as a neuroendocrine tumor and confirmed by immunohistochemistry.

The diagnosis of necrolytic migratory erythema is a matter of great importance, since it might be an auxiliary tool for the early detection of glucagonoma.

DESCRIPTORS: **Necrolytic migratory erythema. Glucagonoma syndrome. Glucagonoma.**

Necrolytic migratory erythema (NME) is a rare skin condition characteristically presented as an irregular annular eruption with a serpiginous advancing border. Bullae may be seen at the centre of the lesions that subsequently erode and become crusted. The lesions occur most commonly on the perineum, distal extremities, lower abdomen, and face[1-4].

NME usually appears as a paraneoplastic process in patients with alpha cell tumor of the pancreas, i.e., glucagonoma. Glucagonoma, in association with hyperglucagonemia, glucose intolerance, anemia, and weight loss, defines the glucagonoma syndrome[3,4].

Less often, NME may have no correlation with glucagonoma and be related to celiac disease, malabsorption, chronic pancreatitis, infection and hepatic cirrhosis, or extrapancreatic glucagon-secreting tumor (renal, duodenal, or pulmonary)[5-12]. We describe a woman with NME associated with glucagonoma syndrome.

CASE REPORT

A 52-year-old white woman with an 8-month history of pruritic and burning skin eruption that rapidly progressed to involve the entire body was referred for evaluation. The patient presented marked fatigue, anorexia, weakness, confusion, and a 20-pound weight loss over the previous 8 months.

She was treated with topical and systemic steroids (prednisone 20 mg/day) for 2 months without clinical improvement. There was no history of alcohol intake or diabetes mellitus.

Examination revealed a cachectic woman with symmetrical erythematous, scaling and crusted annular plaques that were particularly prominent around perineum (Fig. 1). The lesions appeared as urticarial papules and small vesicles on the trunk. Symmetric erythema, blisters, and edema were observed on the legs and feet. Superficial erosions were present in the intertriginous areas. Glossitis and angu-

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lar stomatitis were also noted. The clinical differential diagnosis included zinc deficiency, pellagra, pemphigus vulgaris, and NME.

Examination of biopsy specimens showed an intraepidermal cleft, presence of vacuolated pale epidermal cells with pyknotic nuclei, and neutrophils in the upper epidermis (Fig. 2)—all changes consistent with NME.

A computed tomography scan of the abdomen revealed a 3-cm pancreatic mass (Fig. 3) and multiple metastatic nodules in both lobes of the liver.

The serum glucagon level was markedly increased to 4517.1 pg/mL (normal 50 to 150 pg/mL). Glycemia was increased to 204 mg/100 mL (normal 70 to 100 mg/mL), hematocrit value was 22.1 (normal 35-45), and all serum amino acid levels were decreased. The serum zinc level was within normal limits. With the support of these findings, the diagnosis of NME associated with glucagonoma syndrome was made.

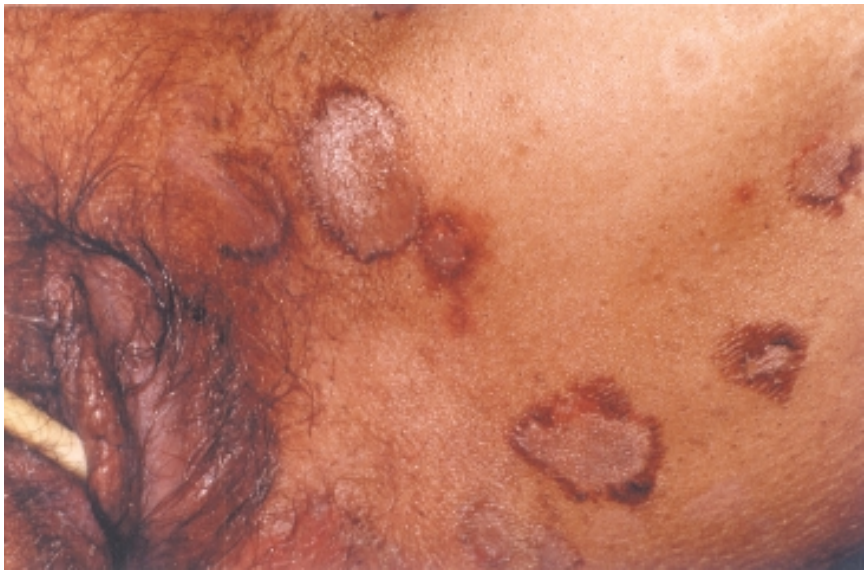

Fig. 1 - Scaling annular lesions around perineum.

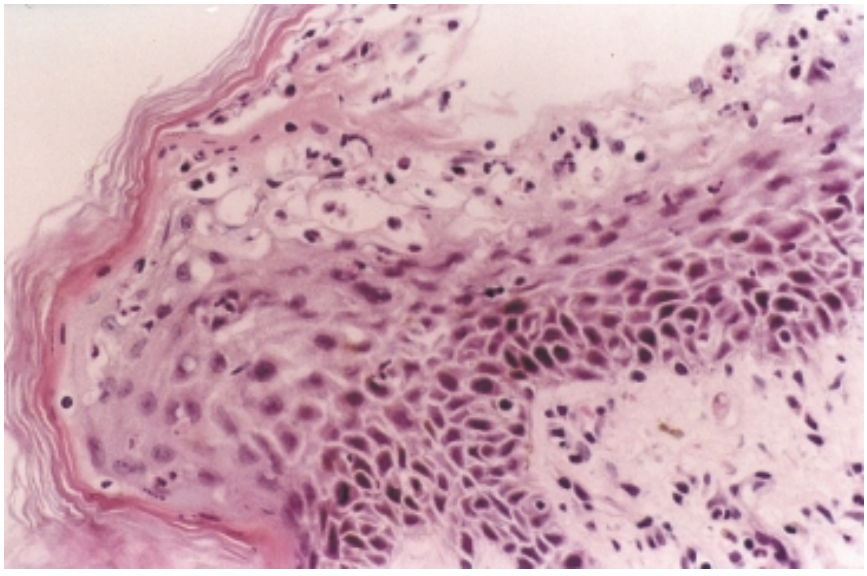

Fig. 2 - Biopsy specimen shows an intraepidermal cleft, vacuolated pale keratinocytes with pyknotic nuclei and neutrophils (HE 400X).

The patient developed acute respiratory distress syndrome and died of acute respiratory failure a week after the admission. No specific treatment was performed.

The autopsy showed 4 pale, hard masses in the body of the pancreas and multiple pale metastatic nodules in both lobules of the liver ranging from 0.5 to 5.0 cm. On microscopic examination, the tumor was composed of small, relatively uniform cuboidal cells with centrally located nuclei and finely granular acidophilic cytoplasm, resulting in defined nests, separated by highly vascularized stroma (solid pattern) (Fig. 4). There was no evidence of glandular or trabecular differentiation. Mitotic figures were scarce. Immunohistochemical staining for chromogranin was strongly positive, while synaptophysin, insulin, glucagon, and somatostatin were negative.

DISCUSSION

Becker et al.[13] described in 1942 a "diffuse progressive epidermal necrotic rash" associated with pancreatic neoplasm. In 1966, McGravan et al.[14] reported hyperglucagonemia in a patient with an eczematoid, erythematous rash, mild diabetes mellitus, anemia, and a glucagon-secreting alpha cell tumor of the pancreas.

Mallinson et al.[2] in 1974 defined the glucagonoma syndrome as presented in 9 patients with diabetes mellitus, anemia, weight loss, a distinctive rash referred as "necrolytic migratory erythema" (NME), and tumor of the islet cells of the pancreas. Glossitis, stomatitis, cheilitis, diffuse alopecia, diarrhea, hypoaminoacidemia, increased incidence of thromboembolism, and psychiatric disturbances complete the glucagonoma syndrome[15].

Our patient had this rare and com-

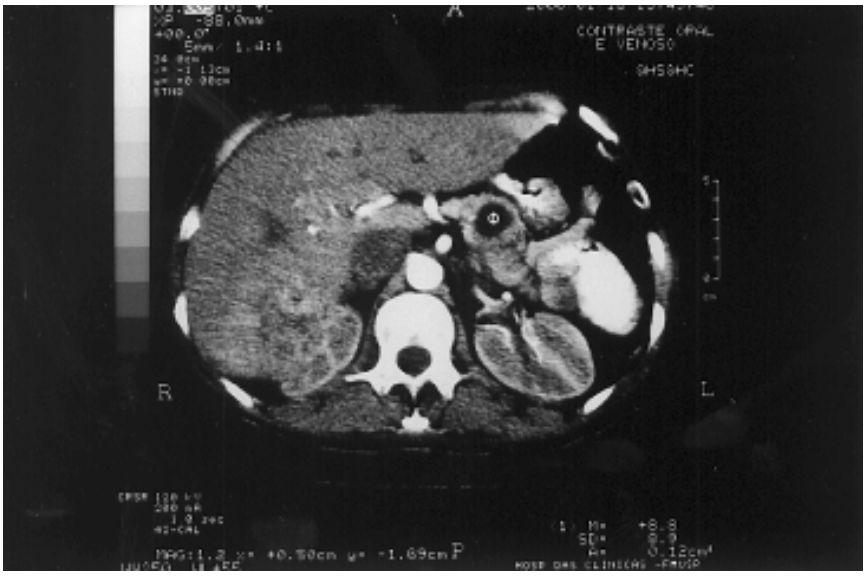

Fig. 3 - Pancreatic mass and metastatic nodules in the liver in computed tomography scan.

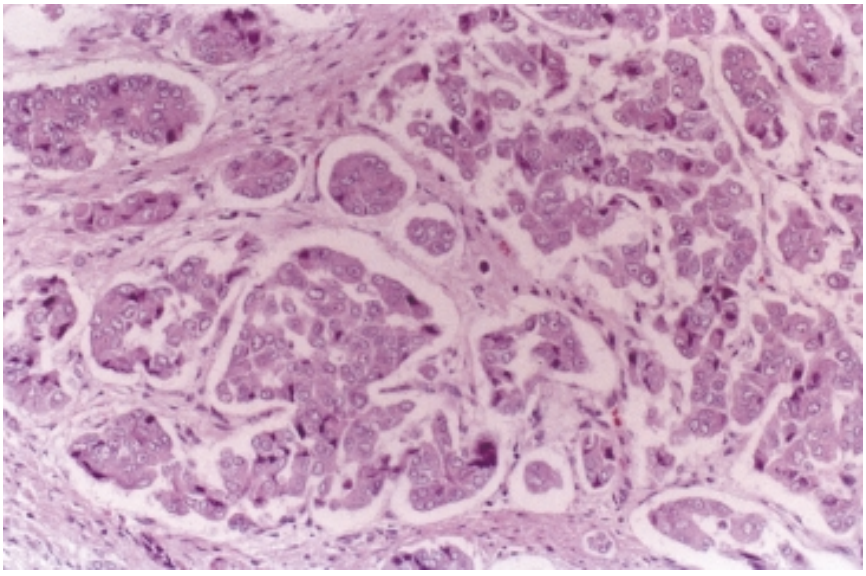

Fig. 4 - Pancreatic neuroendocrine neoplasm with a solid microscopic pattern (HE 100X).

plete syndrome, with metastatic disease at presentation, similar to what is reported in literature[16].

Immunocytochemical findings show that glucagonoma has two distinct types: One associated with the glucagonoma syndrome, presented as a solitary and large tumor, with a solid microscopic pattern, low or lack of immunoreactivity for glucagon and high incidence of malignancy (60% of patients); the other one, not associated with glucagonoma syndrome, has tumors that are often multiple and small, have a gyriform microscopic pattern of growth, are strongly immunoreactive for glucagon, and are always benign[17-20].

The macroscopic and microscopic patterns of our patient's tumor were those of a neuroendocrine neoplasm of pancreatic islet cells. The positive immunohistochemistry for chromogranin confirmed this diagnosis. The negative immunohistochemistry for glucagon does not exclude the possibility of glucagonoma, since the majority of glucagonoma cases associated with this syndrome present low levels or lack immunohistochemical reactivity to glucagon.

There are many theories about the pathogenesis of NME. The effects on the skin of the glucagonoma syndrome that result in NME may be due directly to glucagon itself or to other factors.

The increased level of glucagon as a direct cause of NME is supported by some evidence: the demonstration in vitro that an increased level of glucagon yields greater amounts of epidermal arachidonic acid, which causes the inflammatory changes in the skin[21]; the cure of NME after surgical removal of the tumor, with consequent normalization of serum glucagon levels[22-25]; and the remission of the rash after therapy with somatostatin analogue (octreotide), which is a potent inhibitor of glucagon release[26,27].

However, other evidence fails to link NME with hyperglucagonemia, e.g., the report that only 52% of patients with non-glucagonoma-associated NME had an increased glucagon level[12].

Other theories that could explain the genesis of NME are based on the secondary effects of glucagon. Glucagon stimulates glycogenolysis, gluconeogenesis, ketogenesis, and consequently a systemic catabolic state[28]. The hypoaminoacidemia secondary to increased gluconeogenesis is suggested by some reports as a cause of NME[29,30]. However, several patients cleared the cutaneous lesions after amino acid infusions[29], and some patients with necrolytic migratory erythema had a normal amino acid level[7,31], or did not improve after the supplementation[22].

Delaney and Uff [32] controlled NME using omega-3 triglycerides in a patient with a surgically unresectable glucagonoma. Also, improvement of the

rash has been observed after zinc supplementation in patients who have a low [8,33] or normal serum zinc level[9,34].

The clinical and histologic similarities between NME, hereditary acrodermatitis, enteropathica secondary to zinc deficiency, pellagra, and fatty acid deficiency have been noted[35-36]. The resemblance may be explained by this catabolic state.

Unfortunately, in the present case, the diagnosis was confirmed at a late stage of the disease, and the ideal treatment was not instituted. This case illustrates the importance of early recognition of NME, with its distinctive clinical and histopathologic features, as well as signs and symptoms that compose the glucagonoma syndrome.

These data suggest that the cause for the NME associated with glucagonoma is multifactorial, and it is likely that the postulated theories are not mutually exclusive.

RESUMO RHCFAP/3059

DAL COLETO CC e col. - Eritema Necrolítico Migratório associado à Síndrome Glucagonoma: descrição de um caso. **Rev. Hosp. Clín. Fac. Med. S. Paulo 55**(6):183-188, 2001.

O eritema necrolítico migratório é uma rara condição cutânea que se apresenta como lesões eritematosas, migratórias, com vesículas e bolhas na superfície, evoluindo para cura com hiperpigmentação. É freqüentemente observado em doentes com tumor de células alfa do pâncreas, ou glucagonoma, e quando associado com intolerância a glicose, anemia, hiperglucagonemia, e perda de peso definem a síndrome do glucagonoma.

É descrito o caso de uma paciente do sexo feminino, 52 anos, branca, com eritema necrolítico migratório associado à síndrome do glucagonoma com doença metastática na apresentação, vindo a falecer uma semana após sua admissão. A autópsia mostrou um tumor no corpo do pâncreas diagnosticado como tumor neuroendócrino e confirmado pela imuno-histoquímica. O reconhecimento do eritema necrolítico migratório é de grande importância para a possibilidade de diagnóstico precoce do glucagonoma.

DESCRITORES: **Eritema necrolítico migratório. Síndrome glucagonoma. Glucagonoma.**

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