

Necrolytic migratory erythema associated with hyperglucagonemia and neuroendocrine hepatic tumors

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SUMMARY

We present a 61-year-old man with a 2-year history of persistent disseminated, psoriasiform annular pruritic lesions, acrodermatitis, weight loss, anemia and diabetes. Histopathology of the affected skin showed nonspecific subacute psoriasiform dermatitis. The computed tomographic scan of the abdomen revealed multiple hepatic tumors. Histopathological examination of ultrasound-guided needle biopsy from a hepatic lesion demonstrated a neuroendocrine tumor. Somatostatin-receptor scintigraphy with radio-labelled octreotide confirmed the likelihood of the neuroendocrine nature of the hepatic tumors and excluded the presence of other such lesions throughout the rest of the body, including the pancreas. The serum glucagon level was markedly increased. The diagnosis of necrolytic migratory erythema associated with hyperglucagonemia and neuroendocrine hepatic tumors was made and therapy with the long-acting somatostatin analogue octreotide was started. The skin changes resolved after the initiation of therapy, but no improvement of other symptoms was observed. Having reached the final stage of the disease, which was further complicated by congestive heart failure, the patient died one year later. As no autopsy was performed, we were unable to establish whether the hepatic tumors represented a metastatic process of previously undetected pancreatic glucagonoma or if they were extra-pancreatic glucagon-secreting tumors. The correct diagnosis of necrolytic migratory erythema is important, since it might be the clue for early detection of glucagonoma or of extra-pancreatic glucagon-secreting tumors.

KEY WORDS

necrolytic migratory erythema, hyperglucagonemia, octreotide, neuroendocrine hepatic tumors

Introduction

Necrolytic migratory erythema (NME) is a rare skin condition characterized by an irregular annular eruption with a serpiginous advancing border. The disease was first described in 1942 by Becker et al. who reported a woman with an alpha-cell tumor of the pancreas (1). More than 20 years later, McGavran et al. re-

ported a case with hyperglucagonemia associated with cutaneous changes (2). Wilkinson called the typical skin lesions necrolytic migratory erythema (3, 4). In 1979, Mallinson and co-workers coined the term glucagonoma syndrome to describe the alpha-cell pancreatic tumor associated with a characteristic rash, NME (3). Gluca-



Figure 1. Necrolytic migratory erythema: scaling, erythematous plaques and crusted annular lesions over the trunk and genital area.

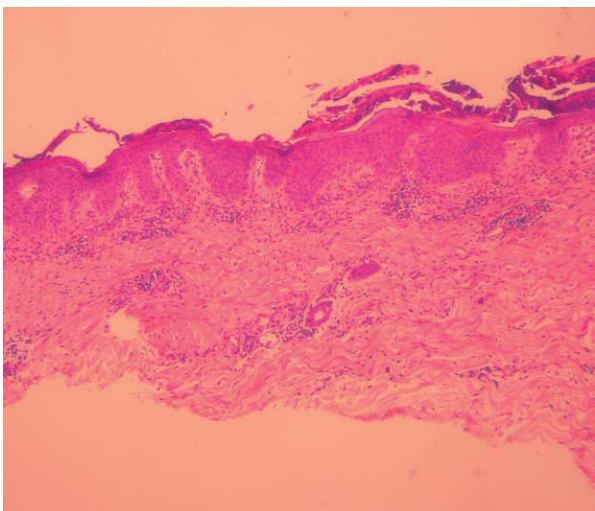


Figure 2. Histopathology, necrolytic migratory erythema: scale crust with neutrophils covering the psoriasiform epidermis, slight spongiosis, subcorneal spongiform pustules, superficial perivascular infiltrate of lymphocytes and neutrophils.

gonoma in association with NME, hyperglucagonemia, glucose intolerance, anemia and weight loss define the glucagonoma syndrome (4, 5). Glucagonomas are among the rarest types of neuroendocrine tumors of the gastroenteropancreatic tract, with an estimated incidence of about 0.5/100.000 cases per year (6). Only rarely is NME not correlated to glucagonoma, but to intestinal malabsorption disorders, hepatic cirrhosis, chronic pancreatitis, inflammatory bowel disease or malignancies (other than pancreatic) (7). The presence of NME in the absence of a pancreatic tumor has been termed pseudo-glucagonoma syndrome. We are describing a male patient with NME associated with hyperglucagonemia and neuroendocrine hepatic tumors.

Case report

A 61-year-old man presented with a 2-year history of persistent pruritic, annular, psoriasiform lesions, which had started on his lower extremities but progressed to involve a large percentage of the total body surface. In addition to the skin changes the patient complained of weight loss (15 kg in one year) and a burning sensation in the mouth, especially after ingestion of alcohol and fruit beverages. One year before abdominal ultrasonography and computed tomography were performed, a metastatic process of the liver was suspected. He refused any further diagnostic procedures until his condition worsened and the weakness, general wasting and skin eruption had progressed. His medical history was otherwise unremarkable and he was receiving no medication. The family history was negative for psoriasis, diabetes mellitus or multiple endocrine neoplasia.

Physical examination revealed a cachectic man with scaling and crusted annular lesions and plaques that were prominent on the lower extremities (Figure 1). Symmetric erythema, edema and superficial erosions were observed on the feet, inguinal area, scrotum and perineum. Prominent scaly erythemas were present in seborrheic areas on the face. Glossitis and angular cheilitis were also noted.

Extensive laboratory testing revealed a normocytic anemia (hemoglobin 77 g/l), an increased erythrocyte sedimentation rate of 73, hyperglycemia (8.7 mmol/l) and a low serum zinc level (8.2 mmol/l).

Because of extensive pruritic skin eruptions, he received topical treatment with regimens including numerous steroids, antifungals and antibiotics in combination with systemic antihistamines, which was unsuccessful. Oral supplementation with zinc (90 mg daily) was not effective. Systemic corticosteroid therapy resulted in a prompt relief of the pruritus and an almost total clearing of the cutaneous eruptions, but the effect was only temporary and relapse was noticed several days

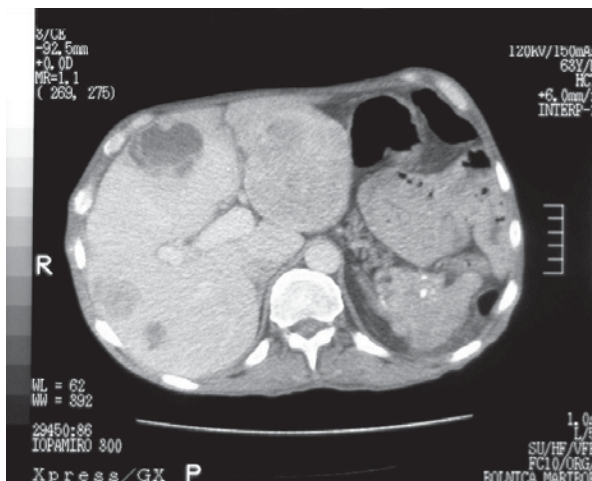


Figure 3. Computed tomography of the liver showing focal hypodense lesions with necrotic changes.

after systemic corticosteroid therapy was stopped.

Histopathological examination of a skin lesion showed a necrotic epidermis with subcorneal pustule and neutrophils in the epidermis (Figure 2). The diagnosis of NME was confirmed. The combination of NME and associated symptoms suggested a paraneoplastic skin disorder linked to a glucagon-secreting pancreatic tumor. An extensive diagnostic exploration was initiated. Abdominal ultrasonography showed multiple round lesions in all liver segments.

An abdominal computed tomography scan reported multiple hepatic tumors, but no pancreatic tumor could be identified (Figure 3). Histopathology and immunohistochemistry of ultrasound-guided needle biopsy from a hepatic lesion revealed a neuroendocrine tumor with strongly positive reaction for chromogranin A. Soma-

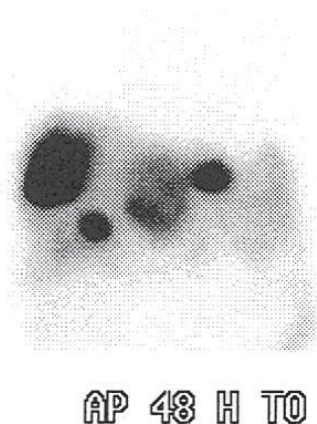


Figure 4. Somatostatin receptor scintigraphy with radio-labelled octreotide revealed three areas of pathologic accumulation of octreotide in the liver.

tostatin receptor scintigraphy with radio-labelled octreotide revealed three areas of pathologic accumulation of octreotide in the liver. The presence of other such lesions throughout the rest of the body, including the pancreas were excluded (Figure 4). The glucagon level was 5075 ng/l, the upper normal limit being 177 ng/l.

Based on these findings, the diagnosis of NME associated with hyperglucagonemia and neuroendocrine hepatic tumors was made. Therapy with the long-acting somatostatin analogue octreotide 30 mg monthly was initiated. NME resolved after the start of therapy, but no improvement of other symptoms was noticed. The patient died one year later after his worsened condition was complicated further by congestive heart failure. Permission for post-mortem examination was refused.

Discussion

Glucagonoma-producing tumors manifest a variety of clinical manifestations ranging from asymptomatic to fully expressed glucagonoma syndrome (8). The most common symptoms are weight loss, anemia, diabetes mellitus, NME and tumor of the islet cells of the pancreas (9). All reported glucagonomas with the cutaneous syndrome occurred in the tail or body of the pancreas, where alpha-cells are normally abundant. The cutaneous manifestations are usually a late finding of the syndrome (10). By the time of diagnosis, in 50% (11) to 100% (8) of patients the metastatic disease is already present and successful treatment is often impossible. In our patient the main clinical symptoms of glucagonoma syndrome were expressed: weight loss, anemia, diabetes mellitus, NME and hyperglucagonemia. In view of the fact that a pancreatic tumor was not found despite extensive diagnostic procedures, our case remains an incomplete syndrome.

Multiple glucagonomas may be associated with multiple endocrine neoplasia syndrome I (MEN I). Glucagonomas due to MEN I syndrome are rare and comprise not more than 3% of glucagonoma syndrome (12). Inheritance is autosomal-dominant. MEN I syndrome includes hyperplasia or tumors of the pituitary, parathyroid, pancreatic islet cells and adrenal cortex. Approximately 80% of glucagonomas associated with the MEN I syndrome are malignant and most often spread hematogenously to the liver.

Acrodermatitis enteropathica (AE), an autosomal recessive form of zinc deficiency typically present in infancy is an entity which clinically and histopathologically mimics NME. AE may occasionally present in adulthood. The serum zinc level was low in our patient, but no clinical improvement of NME after zinc supplementation was noticed.

Liver metastases from neuroendocrine tumors may be found simultaneously with the primary tumor. They

may be found at different times at checkups after resection of the primary tumor or in the absence of a detectable primary tumor. Overall, almost 10% of liver metastases are neuroendocrine in origin (13). Somatostatin-receptor scintigraphy with radio-labelled octreotide and histopathology of a liver biopsy with strongly positive reaction for chromogranin A, revealed a neuroendocrine origin of multiple hepatic tumors in our patient.

The diagnosis was confirmed at a late stage of disease, so an efficient treatment was not instituted. Successful palliative treatment with long-acting somatostatin analogues has been reported in the literature (14), so we decided to treat our patient with octreotide. The skin changes resolved after initiation of therapy but no improvement of other symptoms was noticed. The patient died one year later, after reaching the end stage of the disease, which had been further complicated by congestive heart failure. As no autopsy was performed we were unable to find out whether the hepatic tumors represented a metastatic process of previously undetected pancreatic glucagonoma or if they were primary extra-pancreatic glucagon-secreting tumors. Primary lo-

calization in the liver, although unusual, has been reported for several types of functioning endocrine tumors, including gastrinomas (15, 16), PP-omas (17) and tumors causing hypoglycemia (18, 19) or carcinoid syndrome (20). In some of these cases, the absence of an extra-hepatic primary site was confirmed by autopsy (18, 19). Glucagonomas, like other functioning neuroendocrine tumors, may present as a single hepatic lesion and without specific symptoms (21). In addition, two cases of glucagon-producing endocrine tumors located in the kidney (22, 23) and one in the spleen (24) have been described.

The correct diagnosis of NME is important, since it might be the clue for the early detection of glucagonoma or of extra-pancreatic glucagon secreting tumors. Most patients have the skin disease for at least one year before a correct diagnosis is made (10). In our case two years elapsed before the tentative diagnosis of glucagon-secreting tumor was made, mostly because we were unable to confirm the presence of a pancreatic tumor, which is usually responsible for NME and hyperglucagonemia.

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