Autopsy Case Reports

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Diarrhea: a missed D in the 4D glucagonoma syndrome

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ABSTRACT

Glucagonoma is a rare and slow-growing pancreatic tumor that usually manifests as glucagonoma syndrome. It is mainly characterized by a typical Dermatosis named necrolytic migratory erythema (NME), Diabetes and glucagon oversecretion. Deep vein thrombosis and Depression complete this set. We report the case of an advanced glucagonoma with liver spread, where all these 4D symptoms occurred but a chronic secretory Diarrhea was the most relevant feature. A 65-year-old man was referred to our center to investigate multiple hepatic nodules evidenced by abdominal tomography. He had a recent diagnosis of diabetes and complained of significant weight loss (25 kg), crusted skin lesions and episodes of a large amount of liquid diarrhea during the past 6 months. On admission, there were erythematous plaques and crusted erosions on his face, back and limbs, plus angular cheilitis and atrophic glossitis. The typical skin manifestation promptly led dermatologists to suspect glucagonoma as the source of our patient's symptoms. A contrast-enhanced abdominal computed tomography showed a hypervascularized pancreatic lesion and multiple hepatic nodules also hypervascularized in the arterial phase. Despite initial improvement of diarrhea after subcutaneous octreotide, the patient's impaired nutritional status limited other therapeutic approaches and he died of respiratory failure due to sepsis. His high levels of serum glucagon were not yet available so we performed an autopsy, confirming the diagnosis of metastatic glucagonoma with NME on histology. Chronic diarrhea is not a common feature in glucagonoma syndrome; however, its severity can lead to serious nutritional impairment and set a poor outcome.

Keywords:
Glucagon; Necrolytic Migratory Erythema; Neoplasm Metastasis; Neuroendocrine Tumors; Paraneoplastic Syndromes

INTRODUCTION

The association between skin lesions and multiple hepatic nodules has a broad differential diagnosis, particularly in patients with chronic diarrhea. It is essential to be aware that gastrointestinal tract tumors are related to these three conditions, especially gastric, colonic and pancreatic tumors.[1,2] In this setting, feasible hypotheses are hepatic and skin metastases or paraneoplastic cutaneous syndromes. Often, despite etiological elucidation and treatment, liver spread may determine an unfavourable prognosis.[3,4]

The investigation must be quick. In addition to blood tests and serum tumoral markers, upper digestive

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endoscopy, colonoscopy and contrast-enhanced abdominal imaging are essential. Widespread skin lesions should not be understood as a finding but as part of a systemic disease, so the evaluation of an experienced dermatologist is helpful. We report this fatal case of an advanced glucagonoma, highlighting its severity and systemic involvement.

CASE PRESENTATION

A 65-year-old Caucasian male was referred to our tertiary hospital in order to elucidate the etiology of multiple hepatic nodules detected by abdominal computed tomography (CT). He complained of weight loss during the past 6 months (25 kg), non-pruritic skin lesions on the face and limbs, weakness, sadness, and episodes of a large amount of liquid diarrhea more than 20 times a day without blood or mucus. He was able to ingest less than one daily meal during the last 3 months. He was smoker (20 packs-year) and was on metformin because of a new-onset diagnosis of diabetes mellitus.

On examination the patient had a weakened status (body mass index 14 kg/m^2), with multiple skin lesions (erythematous and brownish plaques and crusted erosions) on his face (Figure 1), back and limbs. He also had angular cheilitis and atrophic glossitis. There were white plaques on the oral mucosa suggesting moniliasis. The liver was hardened and palpable 4 cm below the costal margin and xiphoid process. He had severe asymmetric edema of the lower limbs, and there were no palpable lymph nodes.

Laboratory tests evidenced a relevant normocytic/normochromic anemia with hemoglobin 3.9 g/dL (reference value [RV] 13-16), low serum albumin 1.8 g/dL (RV 3.5-5.2), and low levels of calcium, phosphate, magnesium, sodium, zinc, folate, and potassium. Regarding the severe anemia, the glycosylated hemoglobin was 5.9% (RV 4.0–5.6); the serum C-peptide was unchanged (2.7 ng/mL [RV 0.8–4.2]); and the serum insulin was low (1.5 UI/mL [RV 3.2–16.3]). Other relevant dosages were: prolactin 19 ng/mL (RV 4.0–15.2), ferritin 1,872 ng/mL (RV 30–400), with transferrin saturation at 88%. The liver enzymes, international normalized ratio, bilirubin, parathyroid hormone, and adrenocorticotropin were normal. Serum urea and creatinine were slightly elevated. Viral hepatitis and HIV serologies were negative.

Doppler ultrasonography of the lower limbs showed bilateral deep venous thrombosis. Abdominal CT evidenced a contrast-enhanced lesion between the body and tail of the pancreas measuring 24 mm at its largest diameter (Figure 2A). There were also multiple hepatic lesions with peripheral enhancement in the arterial phase, and a hypodense center, suggesting necrosis (Figure 2B). Carbohydrate antigen 19.9 (CA 19.9) dosage was 413 U/mL (RV < 34); other tumoral markers, such as alpha-fetoprotein and carcinoembryonic antigen (CEA), were unchanged. The stool analysis depicted a fecal osmolar gap of 5.02 Osm / kg H2O (compatible with secretory diarrhea since it is < 50), rare blood red cells, and absence of leukocytes, yeasts, fatty acids, helminths and protozoa. The patient maintained a high fecal discharge even after initial therapeutic measures and parenteral nutrition.

An experienced dermatologist evaluated the patient. Among the differential diagnosis of cutaneous lesions there were pemphigus, malnutrition and vitamin deficiencies in the setting of chronic diarrhea. However, necrolytic migratory erythema (NME) could be a major hypothesis, since it is strongly associated with glucagonoma, which could also encompass the combination of diabetes mellitus, diarrhea, anemia, weight loss and a pancreatic nodule with probable liver metastases.

With this in mind, we performed the dosage of serum glucagon and vasoactive intestinal peptide (VIP), and subsequently initiated subcutaneous octreotide

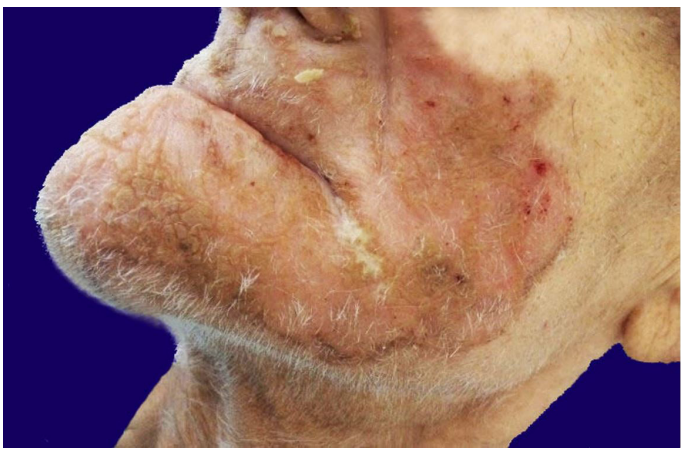

Figure 1. Brownish erythematous scaly lesions with crusts on the perioral region and nasogenic sulcus.

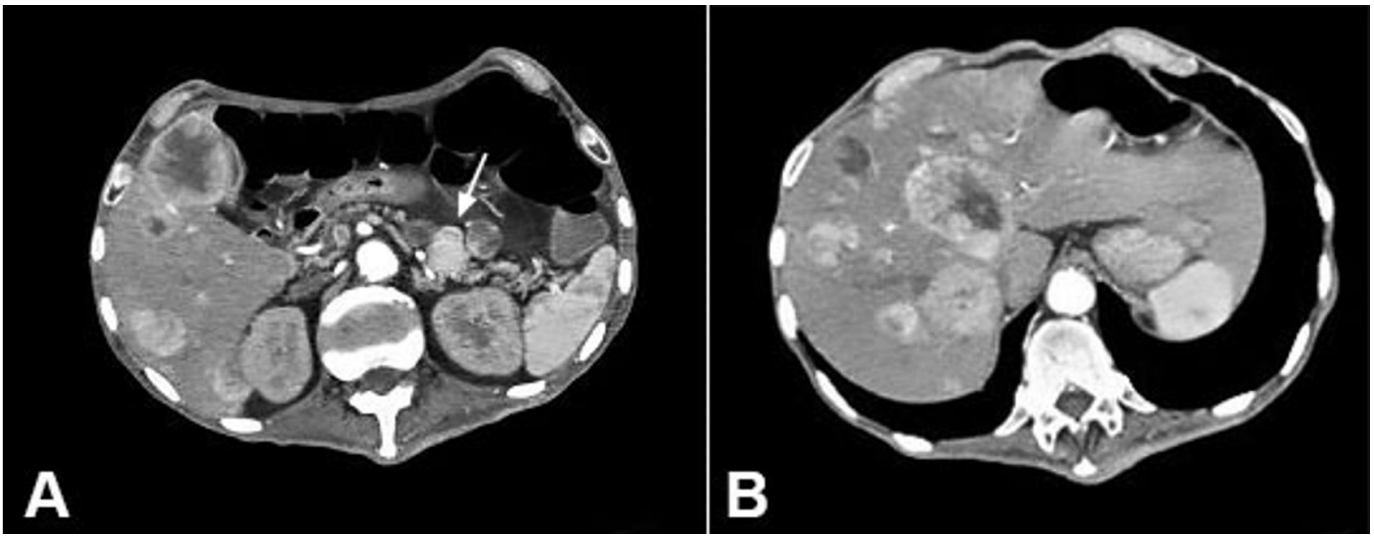

Figure 2. Axial abdominal enhanced CT in the arterial phase showing in **A -** an enhanced pancreatic nodule measuring 24 mm at its largest diameter (white arrow), and multiple hepatic nodules with peripheral enhancement and a hypodense center (necrosis); **B -** multiple hepatic nodules with peripheral enhancement and a hypodense center (necrosis).

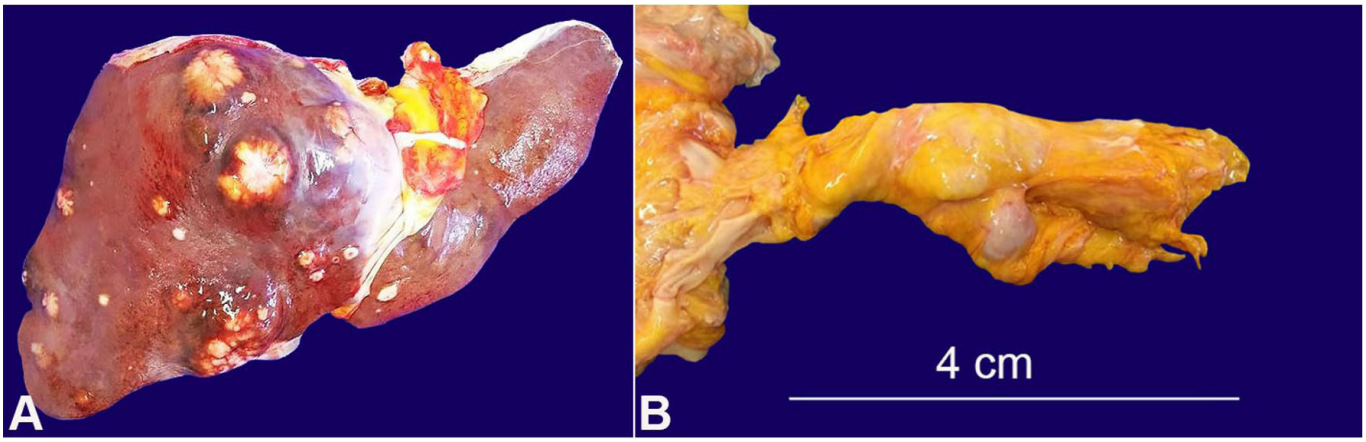

Figure 3. Macroscopic view of the: **A -** liver showing multiple hepatic nodules (metastases); **B -** nodule in the pancreatic body (neuroendocrine tumor).

100 mcg three times a day. There was satisfactory improvement of the diarrhea; however, the patient's condition evolved to septic shock due to pulmonary infection, and he died of respiratory failure 20 days after admission. The VIP dosage was slightly elevated, 49.6 pmol/L (RV < 30) and serum glucagon was 4,354 pg/mL (RV < 208), but we did not yet have this dosage on the day he died, so we decided to perform the autopsy (with his family's consent).

AUTOPSY FINDINGS

There were multiple hardened and well-delimited nodules in the liver – the largest measuring 85 mm (Figure 3A). Between the pancreatic body and tail, we found a brownish solid nodule measuring 28 × 25 × 25mm (Figure 3B) with an enlarged adjacent lymph node measuring 20 × 18 × 18 mm.

Histological analysis evidenced a well-differentiated pancreatic neuroendocrine tumor (Figure 4A), with lymph node and liver metastases, which was confirmed after immunohistochemical staining positivity for CD56 (Figure 4B), chromogranin A (Figure 4C) and synaptophysin (Figure 4D). The proliferating index Ki67 was inconclusive, due to autolysis. Skin lesions histology showed epidermis with marked degenerative changes and superficial necrosis, loss of the granular layer, cytoplasmic balloonisation and vacuolisation of keratinocytes, which was compatible with NME (Figure 5).

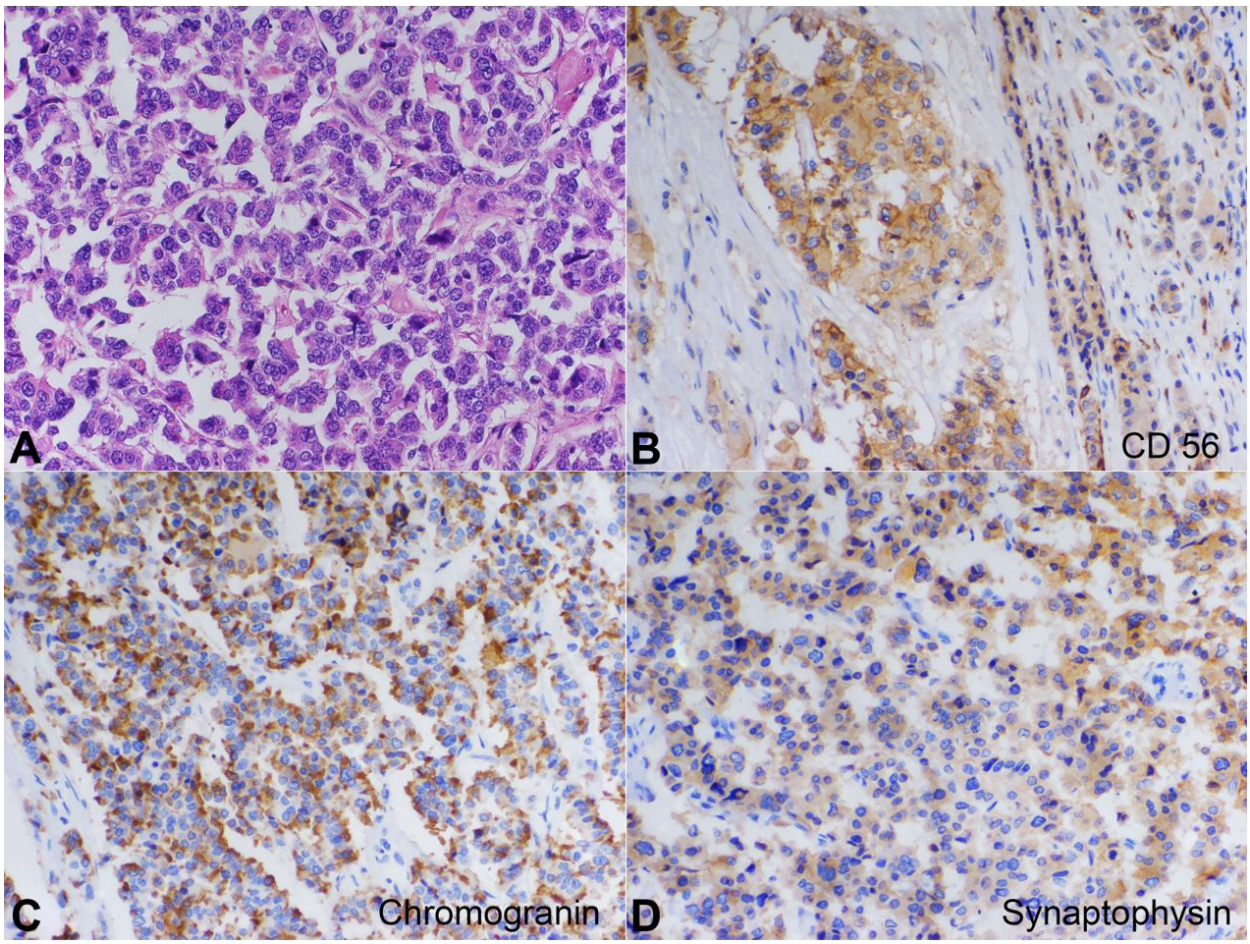

Figure 4. Photomicrographs of the pancreas showing in **A -** nodular and diffuse infiltration of round cells with stippled chromatin, inconspicuous nucleoli, and finely granular cytoplasm (H&E, original magnification ×100); **B -** Immunohistochemical staining positive for CD56 (× 100); **C -** Immunohistochemical staining positive for Chromogranin A (x 100); **D -** Immunohistochemical staining positive for Synaptophysin (× 100).

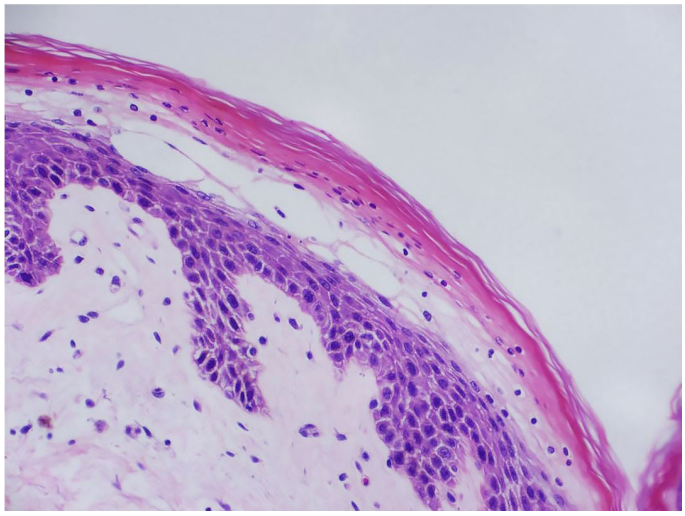

Figure 5. Photomicrograph of the skin showing spongiosis and parakeratotic hyperkeratosis in the upper layer of the epidermis with necrosis, loss of the granular layer, vacuolized and dyskeratotic keratinocytes, compatible with necrolytic nigratory erythema (H&E, original magnification ×20).

DISCUSSION

Among the functioning pancreatic neuroendocrine tumors, the most common are gastrinomas and insulinomas. Glucagonomas are extremely rare, with an estimated global incidence of one case in 20 million people.[5,6] The peak presentation is in the fifth decade of life, affecting men and women in almost equal proportions. Less than 10% of tumors are associated with familial syndromes – more frequently multiple endocrine neoplasia type 1 (typically non-functioning).[3,7,8] Most are sporadic and this presentation has lower survival, since about half of the patients have metastases at diagnosis.[9,10] Achieving effective treatment and reaching higher survival rates remain a major issue.

In approximately 87% of cases, sporadic glucagonoma is located in the body or tail of the pancreas.[11] This tumor has an alpha-cell production

of glucagon,[5,12] and the main clinical manifestation is known as glucagonoma syndrome (GS). It is a systemic condition characterized by the combination of NME, high levels of serum glucagon and hyperglycemia.[10] This was our patient's presentation. There were no additional features to suggest multiple endocrine neoplasia type 1, except for a slight increase in serum prolactin, which was not valued.

NME is a paraneoplastic skin disorder typically presented in up to 70%–80% of the patients with GS.[10] Lesions can be widespread but are usually located in intertriginous areas, perioral region, perineum, lower abdomen, thighs and distal extremities, and may have a migratory course, occurring in spontaneous exacerbations and remissions. Commonly there are annular or irregular eruptions and plaques with superficial epidermal necrosis and crusts, leading to pruritus or pain, with susceptibility to secondary infection. After lesions heal, residual areas of hyperpigmentation and peripheral collarette can remain. The most specific histological feature includes superficial epithelial necrosis of the upper spinous layer with vacuolated keratinocytes.[13] Patients may also present angular cheilitis, glossitis and alopecia.[10] In 90% of cases, NME is associated with glucagonoma but some conditions – usually leading to nutritional impairment – may be involved, such as cirrhosis, cystic fibrosis, inflammatory bowel disease, kwashiorkor, celiac disease and other neoplasms.[7] This rare presentation is known as pseudoglucagonoma syndrome.[5,14]

Other findings of GS include anemia (49.6%), weight loss (66%–96%), diarrhea (30%), abdominal pain (7.5%–10.6%), lower limbs edema, venous thromboembolism (50%) and depression (50%);[3,15-17] these match our patient's presentation. Glucagon-related cardiomyopathy has already been described.[18] GS is known as 4D syndrome (Dermatosis, Diabetes, Deep vein thrombosis and Depression).[17] Diarrhea occurs more frequently in patients with other conditions, such as somatostatinomas, gastrinomas, VIPomas and carcinoid tumors. Multiple etiologies could be associated with that, such as increased motility, malabsorption and bacterial overgrowth. The consequences are hydroelectrolytic disorders, renal disfunction, weight loss and malnutrition.[3] This was the most relevant symptom in our patient and he had also a slightly elevated serum VIP, which may have contributed to it.

Glucagonoma is a slowly progressing tumor, and some patients develop pancreatic adenocarcinoma before the neuroendocrine tumor spreads. Metastases are found in half the patients at diagnosis.[9,10] and occur predominantly in the liver (79%–90%) and lymph nodes (30%–37.8%).[7] Early recognition of GS before liver dissemination can be life-saving,[5,19] with a 10-year survival reaching 100%.[20] However, after it spreads to the liver, survival drops by half.[17] When there is massive hepatic involvement the liver cannot properly metabolize glucagon, icreasing its levels and thereby worsening the symptoms.[17]

Song et al.[12] evaluated 623 reported cases of glucagonoma. The male to female ratio was 0.79 and metastases were detected in 49.2% of patients. These subjects were older than those without metastases upon diagnosis (54.0 vs. 50.8 years old). The average time between initial symptoms and diagnosis of the tumor was 31.4 months. Wei et al.[9] reported six cases of GS in a 17-year database. Most were women (4/6), and the median age at diagnosis was 48.8 years (younger than our patient). NME was found in all subjects and was the first symptom in 67%. Five patients had diabetes mellitus and the other one had impaired glucose tolerance. The whole group had anemia, and the serum glucagon ranged from 245.6 to 1,132.0 pg/mL. The highest value was a quarter of our patient's level.

In a series of 21 patients with GS reported by Wermers et al.[14], eleven were male (52,4%). The median age at diagnosis was 54 years (also younger than our patient). Twenty subjects had already liver spread at diagnosis and the other one had lymph node dissemination. However, just 9/21 patients had tumor-related death, which occurred on average 4.91 years after diagnosis.

Despite the diverse clinical features, the diagnosis of glucagonoma requires evidence of a pancreatic lesion by an imaging examination. As this tumor is often located in the distal pancreas, the role of ultrasonography seems to be limited.[21] Therefore, the most useful methods are contrast-enhanced imaging, such as CT and magnetic resonance.[5,21] Positron emission tomography or octreotide scan scintigraphy may be applicable especially when there is concern for distant disease.[22] In addition to the dosage of serum glucagon, C-peptide and usual laboratory measurements (blood count, lipids, glucose, glycosylated hemoglobin, vitamins, electrolytes, iron, ferritin, hepatic and renal function), hormonal profile must be evaluated, since glucagonomas (as other

islet cell neoplasms) may overproduce multiple hormones, such as insulin, adrenocorticotropin, parathyroid hormone, gastrin and VIP.[3,5,17] High levels of chromogranin A have been associated with advanced disease.[23]

The management of glucagonomas is wide and multifactorial. Hyperglycemia can be controlled using insulin or oral blood glucose lowering drugs. Ketoacidosis rarely occurs since pancreatic beta cells are preserved. Somatostatin analogues (octreotide/lanreotide) have effective suppression on glucagon secretion, so it is used to improve GS symptoms, such as diarrhea and skin lesions.[10,24] However, it may work through other mechanisms as some cases have had a response independent of the decrease in glucagon levels. The use of somatostatin analogues is a well-tolerated and safe therapy, but it has lower effectiveness in the management of diabetes mellitus and does not reduce the incidence of venous thrombosis, which requires prophylactic low doses of heparin.[24]

Nutritional support is necessary, since patients have usually a relevant weight loss.[22] Total parenteral nutrition with amino acid and caloric supplementation may be used to counteract the catabolic effects of high glucagon.[19] Surgical resection of the pancreatic nodule is indicated whenever possible.[25-29] After tumor resection, the symptoms of GS commonly decrease.[22] Unfortunately, less than 15% of patients with liver spread have the possibility of surgical cure, requiring additional therapy.[21] Interferon-alpha, everolimus and sunitinib are useful, especially in the presence of liver metastases. Embolisation, chemoembolisation and radioablation may be performed with satisfactory outcomes.[2,3,28] Radioisotope therapy can also benefit some patients.[6,30]

When patients are not able to undergo surgery, systemic chemotherapy can be conducted, particularly streptozotocin and doxorubicin.[5] Cryoablation is an option to treat the pancreatic tumor and NME, but it requires additional studies to prove efficacy.[10] After pancreatic resection, liver transplantation should also be considered in cases with clinically controlled disease, even in the presence of hepatic metastases.[18,31]

Our patient was older than most of the previously related cases of sporadic glucagonoma. He could not undergo surgery because of his impaired nutritional status. He had a delayed diagnosis. He was not receiving satisfactory nutrition and did not experience episodes of hypoglycemia probably because of his very high levels of glucagon. When he was finally admitted to hospital, the diagnosis was suspected and treatment was promptly initiated; however, we were not able to prevent his unfavourable but presumed outcome.

CONCLUSION

Dermatosis, Diabetes, Deep vein thrombosis and Depression characterize the 4D GS – a main manifestation of glucagonomas. Necrolytic migratory erythema is the most specific presentation but the systemic involvement of this syndrome must be broadly recognized. Our intention is not really to change the acronym '4D' to '5D', but to emphasize that although chronic secretory diarrhea is not such a common clinical feature, it leads to severe nutritional impairment and can set a poor outcome, especially in elderly patients.

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The authors retain an informed consent signed by the patient's next-of-skin authorizing the autopsy and data publication. The manuscript is by the institutional Ethics Committee.

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