Malign cystic glucagonoma presented with diabetic ketoacidosis: case report with an update

S M Fenkci¹, G Fidan Yaylali¹, Y Sermez¹, H Akdam¹, N Sabir² and S Kiraç³

¹Pamukkale University, School of Medicine, Departments of Endocrinology and Metabolism, Pamukkale University Hospital, Kinikli, Denizli, Turkey
²Pamukkale University, School of Medicine, Departments of Radiology, Pamukkale University Hospital, Kinikli, Denizli, Turkey
³Pamukkale University, School of Medicine, Departments of Nuclear Medicine, Pamukkale University Hospital, Kinikli, Denizli, Turkey

(Requests for offprints should be addressed to G Fidan Yaylali; Email: guzinf@yahoo.com)

Abstract

A 44-year-old woman was diagnosed with type II diabetes in 1998 and 1 year later she developed necrolytic migratory erythema, which is a specific skin lesion of glucagonoma. During the clinical investigation, a nodular 6 cm mass in the distal pancreatic region and multiple cystic liver metastases were found. She was operated on, and glucagonoma was detected and the long-acting, repeatable, octreotide treatment was started. 3 years after resection of a pancreatic glucagonoma she presented to a hospital emergency department with diabetic ketoacidosis. Hepatic multiple cystic metastases were visualized by computed tomography. During hospitalization she developed severe pulmonary embolism and deep-venous thrombosis of the lower extremities. Indium-labeled octetide scintigraphy showed multiple cystic lesions in the liver with additional lesions in the iliocecal region, which had not been visualized by computed tomography. Despite somatostatin therapy the tumor had expanded in the liver. Arterial chemoembolization was performed but 6 months later she died.

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Introduction

Glucagonoma syndrome is a rare malignant disorder which comprises hyperglucagonemia, diabetes mellitus, necrolytic migratory erythema and hypo-aminoacidemia in the setting of a glucagon-producing, α-cell tumor of the pancreas (Werners et al. 1996). The incidence has been estimated to be 1 in 20 million per year (Werners et al. 1996). Necrolytic migratory erythema (NME), which is the skin condition of the syndrome, typically presents with irregular annular eruption and a vertiginous advancing border (Werners et al. 1996). Glucagon itself is responsible for most of the observed signs and symptoms, and its induction of hypo-aminoacidemia is thought to led to necrolytic erythema.

The optimal treatment for glucagonoma is debulking surgery. Removal of the primary tumor with a distal pancreatectomy brought evident relief of all clinical symptoms for 1- and 2-year periods. But about 50% of the tumors have metastasized by the time of diagnosis (El Rassi et al. 1998). We present a case of malign cystic glucagonoma with widespread NME, pulmonary and deep-vein thrombosis and diabetic ketoacidosis, all of which are hardly ever seen together.

Case report

3 years after resection of a pancreatic glucagonoma a 44-year-old woman presented to a hospital emergency department with ketoacidosis. She had been diagnosed with type II diabetes in 1998 and 1 year later an annular skin eruption had developed on her hands which progressed to her entire body. In the meantime, computed tomography (CT) of the abdomen had demonstrated a nodular 6 cm mass in the distal pancreatic region and multiple cystic liver metastases that were 4 cm in diameter. She underwent pancreatectomy and splenectomy. Histological examination
Figure 1  Suppurative skin lesions of hands, severe onychoschizia.

Figure 2  Necrotic migratory erythema, suppurative necrotic lesions with irregular annular margin.
had confirmed a malignant endocrine tumor, which was immunohistochemically positive for chromogranin A. After 3 years of treatment with long-acting, repeatable, octreotide (Sandostatin LAR) the liver metastasis did not show any progression and her symptoms were relieved.

In 2003 she was hospitalized with diabetic ketoacidosis. The physical examination revealed tachycardia and 3 cm palpable liver from the costal margin. Biochemical examination showed the serum total protein and albumin levels of 5.8 and 2.2 mg/dl, Gamma-glutamyltransferase (GGT) of 191 IU/l and lactate dehydrogenase of 190 IU/l. Hemoglobin level was 9 mg/dl. She was given i.v. fluids, insulin and octreotide. CT of the abdomen demonstrated cystic metastatic lesions in the liver of up to 7 cm in diameter. Serum glucagon level was 33 500 ng/l (50–250 ng/dl). 2 days after her admission she developed marked dyspnea and conspicuous pretibial edema. Her duplex ultrasonographic examination and ventilation perfusion scintigraphy showed deep-vein thrombosis and pulmonary embolism. She was heparinized and amino acid solutions were given. The skin lesions regressed remarkably. Then suppurative extensive skin lesions in the groin, perineum and lower extremities developed, which were associated with severe onychoschizia (Figs 1 and 2). Essential amino acid solution, fatty acids and zinc were given. Scintigraphy with $^{111}$indium-labeled octreotide revealed multiple cystic lesions in the liver and additional lesions in the iliocecal region (Figs 3 and 4). CT of the abdomen was also performed and demonstrated an increase in the size and number of

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**Figure 3** Scintigraphy with $^{111}$indium-labeled octreotide, multiple cystic lesions in the liver and additional lesions in the iliocecal region (Left panel: anterior, Right panel: posterior abdominal view).
hepatic metastases (Fig. 5). Hepatic arterial chemoembolization was performed but she only lived for another 6 months.

Discussion

Glucagonoma syndrome is a rare disorder that was first defined by Mallinson et al. (1974). It is characterized by a necrolytic migratory erythema, angular stomatitis, painful glossitis, a normochromic normocytic anemia, mild diabetes mellitus, weight loss and neuropsychiatric disturbances. As in the case presented here cystic glucagonoma is a unique variant of classic glucagonoma. 10–30% of patients may present with a thromboembolic phenomenon, deep-vein thrombosis and pulmonary embolism, which often lead to the death of the patient. The response of our case to antiaggregant therapy was excellent.

The diagnosis is made by the finding of a pancreatic α-cell tumor, most of which have metastasized by the time of diagnosis. Tumor and hepatic metastases can be visualized by CT. Somatostatin receptor scintigraphy is useful for consistent supervision of somatostatin receptor expression and dissemination of the tumor metastases. It is frequently used as a complementary method to conventional imaging such as CT and magnetic resonance imaging (MRI; Krausz et al. 1998). The positive immunohistochemistry for chromogranin confirms the diagnosis. The negative immunohistochemistry for glucagon does not exclude the possibility of glucagonoma, since the majority of glucagonoma cases are associated with low levels or even a lack of immunohistochemical reactivity to glucagon. Diagnosis can be confirmed with high plasma glucagon concentrations in the absence of any other cause, such as renal failure or severe stress. In our patient the last CT imaging visualized multiple
hepatic metastases but additional iliocecal lesions were shown by somatostatin-receptor scintigraphy.

Although the optimal treatment for glucagonoma is surgery, 50% of the tumors have metastasized by the time of diagnosis (El Rassi et al. 1998). Streptozocin, the usual chemotherapeutic agent for these tumors, is quite toxic and frequently unsuccessful. Another toxic chemotherapeutic mediator is dimethyltriazeno-imidazol carboximide (DTIC) and can be used for recurrence after operation (Prinz et al. 1981). Long-acting somatostatin analogues, which are potent inhibitors of glucagon release, have been proven effective in suppressing glucagon secretion from glucagonomas and controlling the metastatic growth. Since the tumor is slow growing, remission can be obtained by hepatic artery embolization to shrink hepatic secondary tumors or cytoreductive surgery can be applied with the combination of 5-fluorouracil and streptozotocin (Prinz et al. 1981). Combined treatment with somatostatin analogues (sandostatin LAR) and hepatic arterial chemoembolization was applied with good results in order to relieve the symptoms, to reduce plasma glucagon levels and to prevent progression of metastatic disease. In our presented case disease progression had been controlled with 3-year treatment of octreotide and then remission had been achieved with hepatic arterial chemoembolization. The patient’s symptoms had improved.

The lesions of the glucagonoma syndrome that result in NME may be due directly to glucagon itself or to other factors such as the liver disease, hypo-amino-acidemia, and fatty acid and zinc deficiencies (Alexander et al. 2002). In the presented case the NME responded well to an i.v. infusion of essential fatty acids and amino acids, and to oral zinc.

The development of diabetic ketoacidosis is an extraordinary complication of a glucagon-secreting pancreatic islet cell neoplasm with only six reported cases in the literature, and the pathophysiology remains unknown (Anthony et al. 1995). Soga et al. (1998) collected a total of 407 cases from the international literature. They reported that the 10-year survival rate was 51.6%. Our case had lived approximately 48 months.

In conclusion, the presented case comprises rare clinical conditions associated with glucagonoma such as ketoacidosis and cystic liver lesions. Somatostatin receptor scintigraphy was effective in demonstrating extrahepatic lesions that could not otherwise be visualized by conventional imaging techniques.

References
Alexander EK, Robinson M, Staniec M & Dluhy RG 2002 Peripheral amino acid and fatty acid infusion for the treatment of necrolytic migratory erythema in the

Figure 5 CT of the abdomen, extensive liver metastases in the liver, up to 7 cm in diameter.