Clinical case

Association of malignant insulinoma and type 2 diabetes mellitus: 
A case report

Insulinome malin et diabète de type 2 : à propos d’un cas

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Résumé

Nous rapportons un cas d’hypoglycémies récurrentes dues à un insulinome malin chez une patiente, dont le diabète de type 2 était correctement équilibré pendant des années avec le même traitement antidiabétique oral.

Une patiente de 79 ans était admise pour des hypoglycémies à répétition. Elle présentait un diabète de type 2 depuis l’an 2000. Son HbA1c était à 7,8 % et à 5,8 % après le début des hypoglycémies devenant sévères, malgré la diminution, puis l’arrêt du glicazide. À l’admission, l’insulinémie, les taux de peptide-C et de pro-insuline étaient inappropriés par rapport à la glycémie. Le scanner abdominal montrait de nombreux nodules de type kystique dans le pancréas et le foie. La biopsie hépatique retrouvait un carcinome de type neuroendocrinien bien différencié, positif pour la chromogranine et négatif pour l’insuline. Les hypoglycémies étaient améliorées par l’administration de diazoxide, lanréotide et perfusion de glucosé. Une chimioembolisation était prévue, mais annulée du fait de l’apparition d’œdèmes, d’une hyponatrémie et d’une hypo-osmolarité associés à une détérioration clinique rapide entraînant une défaillance multiviscérale. La patiente devait décéder en quelques jours.

L’association d’un diabète et d’un insulinome est exceptionnelle. Les insulinomes malins sont de mauvais pronostic, avec une survie d’environ deux ans, souvent moins en cas de lésions secondaires hépatiques au diagnostic. L’association à un diabète retardé ce diagnostic, mais n’altère pas le pronostic. Le lanréotide s’est montré inefficace chez notre patiente malgré les bonnes réponses décrites dans la littérature. Des défaillances cardiaques, hépatiques ou rénales ont été décrites avec le diazoxide indépendamment des doses administrées ; cela peut expliquer le décès rapide de la patiente.

Le diagnostic d’insulinome doit être évoqué lors d’hypoglycémies récentes et répétées chez un patient diabétique, en particulier si celles-ci persistent après l’arrêt des hypoglycémiants oraux.

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Abstract

We report a case of recurrent hypoglycemia due to malignant insulinoma in a type 2 diabetic patient correctly controlled for years with the same doses of oral antidiabetic agents.

A 79-year-old woman was admitted for recurrent severe hypoglycemia. She had a history of type 2 diabetes since 2000. HbA1c was 7.8% when she reported mild hypoglycemia and 5.8% when recurrent hypoglycemia appeared despite progressive diminution of glicazide. Severe hypoglycemia continued despite interrupting diabetes medications. At admission, results showed inappropriately elevated insulin, C-peptide and proinsulin levels despite significant hypoglycemia. CT scan showed “cystic” nodes in the pancreas and in the liver. Liver biopsy found a well-differentiated neuroendocrine carcinoma with positive staining for chromogranin A and negative staining for insulin. Hypoglycemia improved with diazoxide, lanreotide and dextrose infusion. Liver chemoembolization was planned. Severe edema, dyspnea, hyponatremia, and hypo-osmolarity occurred. The patient’s clinical status deteriorated rapidly with severe cardiac, renal and hepatic failure. She died in a few days. Association of diabetes mellitus and insulinoma is extremely rare. Malignant insulinoma survival is less than two years, shorter when hepatic localizations are present at diagnosis. Association of diabetes with insulinoma delays the diagnosis, but does not

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alter prognosis or favor carcinoma frequency. Lanreotide was inefficient in our patient despite good responses described in the literature. Heart, respiratory and renal failures have been described with diazoxide independently of the doses; this may in part explain the rapid death. Insulinoma should be considered as a cause of unusual and recurrent hypoglycemia in a diabetic patient especially if it persists after interrupting antidiabetic agents.

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Mots clés : Insulinome malin ; Diabète de type 2 ; Toxicité du diazoxide

Keywords: Malignant insulinoma; Type 2 diabetes; Diazoxide toxicity

1. Introduction

Insulinoma is a rare neuroendocrine tumor (four cases/10^6 patients per year) and usually occurs in otherwise healthy people; less than 10% are malignant [1]. In a diabetic patient treated with a hypoglycemic agent, hypoglycemia may be very common and the diagnosis of insulinoma may be delayed. The diagnosis must be considered if hypoglycemia remains frequent despite the withdrawal of hypoglycemic agents. This case illustrates the occurrence of recurrent hypoglycemia in a patient with longstanding type 2 diabetes well controlled for several years with the same agents. This was a case of rapidly fatal malignant insulinoma, the patient dying less than three months after the first hypoglycemic symptoms.

2. Case report

A previously active 79-year-old, type 2 diabetic woman for seven years, was admitted for recurrent severe hypoglycemia without any modifications in treatment (glicazide 30 mg bid and metformin 850 mg tid) for suspicion of excessive diabetic treatment.

The patient had a history of high blood pressure (treated by lisinopril/hydrochlorothiazide 20/12.5 mg and nifedipine/atenolol 20/50 mg per day), hypothyroidism after a thyroid resection for adenoma (treated by levothyroxin 75 μg per day), in situ cancer of the left breast with mammectomy (treated by tamoxifen citrate 20 mg per day) and hysterectomy for fibroma.

The patient had experienced hunger sensations in the late afternoons for several months. Four weeks prior to admission, such sensations began to be more frequent, with dizziness and asthenia. At that time, HBA1c was 7.5%.

Then, the patient began to suffer from multiple moderate hypoglycemic episodes in late afternoon despite progressive tapering of glicazide doses. HbA1c levels had dropped to 5.8%. All diabetes medications were stopped, but severe hypoglycemic episodes remained. Dietary management based on frequent snacks could not prevent these episodes.

The patient was transferred to our unit of endocrinology. She complained of marked asthenia, her height was 160 cm, her weight 67 kg (Body Mass Index: 26.3 kg/m²), blood pressure was 120/60 mmHg, and pulse rate was 60 per minute. The physical examination was otherwise unremarkable.

Laboratory testing at admission (Table 1) showed inappropriately elevated insulin, C peptide and proinsulin levels, despite significant hypoglycemia and high liver enzyme levels. Cortisol level was appropriate for the glucose level. Markers of neuroendocrine tumors were positive. High level of CA 19-9, marker of pancreatic exocrine tumor, could be explained by hepatic cholestasis. Urinary assays of different sulfonylurea compounds were negative. Hypoglycemia rapidly became more and more severe (Table 2).

The abdominal ultrasound imaging and the abdominal computed tomography scan showed nodes in the body and tail of the pancreas and numerous liver cystic nodes from 3 to 30 mm with necrotic centers (Fig. 1). A liver biopsy showed metastasis of a well-differentiated neuroendocrine carcinoma, with a very positive staining for chromogranin A. No positive staining was found for insulin, glucagon, gastrin nor somatostatin.

Hypoglycemic episodes improved with progressively increased doses of diazoxide to 250 mg bid, associated with lanreotide LP, 30 mg per 15 days and dextrose 1000 ml per day.

Due to the numerous liver metastases, liver chemoembolization was planned to decrease the tumor burden. After one
Table 2
Glucose and insulin levels follow-up

<table>
<thead>
<tr>
<th>Dates</th>
<th>Plasma glucose N: 55–100 mg/dl</th>
<th>Insulin N: 2–15 μU/ml, IRMA</th>
<th>C peptide N: 0.8–2.9 μ g/l, RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>18/08</td>
<td>51</td>
<td>45.1</td>
<td>ND</td>
</tr>
<tr>
<td>19/08</td>
<td>42</td>
<td>60.8</td>
<td>7.1</td>
</tr>
<tr>
<td>20/08 (lanreotide and diazoxide)</td>
<td>24</td>
<td>60.9</td>
<td>6.8</td>
</tr>
<tr>
<td>02/09</td>
<td>32</td>
<td>105.0</td>
<td>8.36</td>
</tr>
</tbody>
</table>

A week of diazoxide treatment, edema, dyspnea, anorexia and oliguria were observed associated with weight gain of 7 kg. Laboratory data showed hypo-osmolarity with hyponatremia (108 mmol/l, N: 135–145), hypochloremia, hypoalbuminemia and normal level of urea (5.1 mmol/l, N: 2.5–7). Sodium urinary excretion was 121 mmol per 24 h, N: 40–220). The patient was euthyroid. She was transferred to an intensive care unit, where the diagnosis of SIADH linked to carcinoma was ruled out since, hydric retention, as a classical adverse effect of diazoxide, was retained. After intravenous furosemide treatment and infusion of hypertonic solution, patient status improved transiently. After her transfer to the oncology unit for the chemoembolization, the patient’s condition deteriorated rapidly with severe cardiac, renal and hepatic failures. She died a few days later from liver failure.

3. Discussion

The association of diabetes mellitus and insulinoma is rare [2–8].

To our knowledge, the few cases of type 2 diabetes reported were usually associated with benign tumors. Insulin carcinoma in type 2 diabetic patients is extremely rare: in a review of literature, among 17 cases of insulinoma, only five were malignant [9].

Malignant insulinoma accounts for about 10–16% of all insulinomas. Survival is less than two years after surgery and classically even shorter when liver localizations are present at diagnosis [1]. As for all endocrine tumors, pathological examination is unable to diagnose precisely the possible malignancy. Negative staining of liver metastasis for insulin does not exclude diagnosis of malignant insulinoma since in neuroendocrine tumor metastasis can have a differential secretion in comparison with a primary tumor. Diagnosis of insulinoma is difficult in the diabetic patient, the first hypothesis being an excess dose of diabetic medications. While the association of diabetes with insulinoma delays the diagnosis, it does not alter the overall prognosis nor favor malignancy. In the seven cases of insulinoma associated with type 2 diabetes reported by Svarberg, all patients returned to diabetes state after surgery. There could be a possible association between insulinoma and family history of diabetes. Analysis of family history of diabetes in a series of insulinomas highlights that one-third of subjects had an antecedent of diabetes in their family [10]. In case of secondary lesions, surgery has to be completed by a medical treatment (diazoxide, somatostatin analogues, chemotherapy). This treatment usually controls the hypoglycemia transiently and diazoxide has the greatest long-term benefits on hypoglycemia [2].

Despite some reports of long-term remission and sustained tumor volume decrease, somatostatin analogs are usually described to have a low efficiency in malignant insulinoma and the most effective therapy on tumor volume is chemoembolization [9]. In the reported case, lanreotide was efficient during the first three days. The only efficient treatment was diazoxide. Diazoxide is a mitochondrial adenosine triphosphate sensitive potassium channel opener. It also inhibits insulin secretion by avoiding membrane depolarisation of beta cells. Unfortunately, this treatment can produce toxic effects, as described [11]. Heart, respiratory and renal failures have been described with diazoxide independently of the doses administered; this may in part explain the death of our patient before a chemoembolization could be performed.

The toxicity of diazoxide is not directly related to the dose, but a toxicity index has been proposed (dose of diazoxide × the insulin/glucose ratio) [12]. If this index is more than 1533, toxicity may develop. In the reported case, the patient had an index of 2903 and developed multiple organ failure.

In our case, chemoembolization had been proposed as a palliative treatment because of the inefficiency of somatostatin analog [13]. This method has different purposes: to inhibit

Fig. 1. Abdominal CT scan, at admission, showing pancreatic tumor and multiple metastases.
tumor growth, to control hypoglycemia, and to improve patient survival [14]. Unfortunately, it could not be performed in our patient.

4. Conclusion

Insulinoma should be considered as a cause of unusual and recurrent hypoglycemia in longstanding type 2 diabetic patients, especially when the same doses of oral antidiabetic agents have correctly controlled glycemia and hypoglycemia persists after withdrawal of glucose-lowering agents.

References