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Metastatic insulinoma – prolonged survival after multimodal approach

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Summary

Background:

Metastatic insulinoma is a disease associated with a poor life expectancy.

Case Report:

The case of a presently 68 year old female with malignant, metastatic insulinoma is reported. Due to severe clinical symptoms surgical tumor mass reduction was conducted. Furthermore the patient underwent a chemotherapy using streptozotocine and fluorouracil. After two years without any symptoms, the remaining hepatic metastases increased in size and again hypoglycemias occurred. To reach an asymptomatic state and further reduction in tumor mass, the decision was made for transarterial chemoembolization with streptozotocine. After the first treatment the patient was hypoglycemia – free for 3 months, after another more extensive chemoembolization the patient is presently symptom free for 8 months.

Conclusions:

Since the diagnosis of extended disease was established, the patient has survived for 36 months. We regard this as the result of a multimodal approach and the extensive use of local tumor therapy. The different therapeutic options for local tumor therapy are reported and discussed.

key words:

metastatic insulinoma • transarterial chemoembolization • tumor mass reduction • hypoglycaemia • survival

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BACKGROUND

With an incidence of 1:500000, insulinomas are rare, mostly benign tumors. Multiple adenomas are reported in about 20%. Women are twice as likely to be affected as men; the peak age of occurrence is the 5th decade. The Whipple Triad is typical for an insulinoma: fasting induces blood sugar levels below 50 mg/dl with an improvement of the clinical symptoms by an application of glucose.

10% of the insulinomas are associated with the MEN syndrome type 1 (multiple endocrine neoplasia type 1). In this autosomal-dominant disease pattern the Menin gene, a tumor suppressor gene located on chromosome 11(11q13) has a loss in function [1]. Insulinomas within the entity of MEN more often have malignant character than singularly occurring insulinomas.

In benign insulinomas, surgical enucleation or resection is the first line therapy. Given a complete excision no further therapy is required. If complete resection is not possible, pharmacological treatment is required. In malignant insulinomas with metastatic growth a surgical debulking should be conducted. This leads to a mass reduction of the tissue secreting insulin and its precursors, easing endocrine symptoms caused by the tumor. Due to the possibility of multiple tumours in the pancreas a careful examination with intraoperative ultrasound or bidigital palpation of this organ is recommended during the operation.

A conservative approach is the application of somatostatin analogues or diazoxide. The analogues bind reversibly to somatostatin receptors (especially subtype 2), and inhibit hormone release. However, diazoxide, although more cost-effective can cause severe side effects in some patients, like massive oedemas. Chemotherapeutic treatment regimes of malignant insulinomas are usually based on streptozotocine. This leads to a dose dependent destruction of beta cells. In addition, fluorouracil or doxorubicine are administered [2].

Further therapeutic options are based on local tumour mass reduction regimens and will be discussed later on. However, the plethora of regimens underlines the dissatisfying results of the present therapy of malignant insulinomas.

CASE REPORT

After an episode of unconsciousness a 65 year old, normal weight (56 kg, 163 cm, BMI 21.1 kg/m²) female was delivered into the neurological department of our hospital. She did not show signs like enuresis, toddler's palsy or a bitten tongue. An intercerebral bleeding or an ischaemia were radiologically excluded. However, the low blood glucose (initially 12 mg/dl) level did not rise adequately during an infusion with glucose 5%. The patient was transferred to the internal department. She denied addephagia or any other pre-existing disease, the body weight had remained constant for years.

Sulfonylurea intake had been excluded in urine analysis. The fasting insulin levels (39.4 uE/ml; N. 1-20) and C Peptide (5.72 ng/ml N. 0.78–1.89) were increased. We abdicated on a fasting provocation due to the already low blood glucose levels. The values for thyroid and adrenal hormones

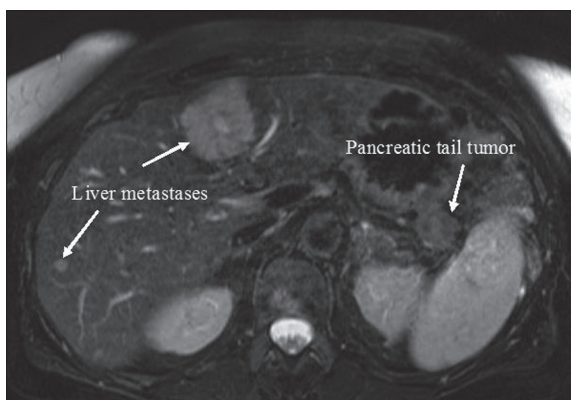


Figure 1. Abdominal MRI: Pancreatic tumor, invading the spleen, hepatic metastases.

(before and after ACTH stimulation) were within normal limits. Chromogranin A was elevated (8700 ug/l N. <100).

In magnetic resonance imaging and in ultrasonography several intrahepatic lesions were localized. Furthermore, a tumor in the pancreatic tail infiltrating the spleen could be detected. (Figure 1) Metastases were furthermore found in the lumbar spine and in the lower lobe of the right lung.

In a biopsy taken from a hepatic lesion, a neuroendocrine carcinoma, with positive staining for insulin, could be verified. The tumor was well differentiated. The proliferation rate, measured by counting MIB 1 positive nuclei, was less than 5%.

Under administration of Octreotide (100 ug, three times a day) and 24h Glucose infusions, hypoglycemias (as low as 14 mg/dl) recurred. Thus, a decision was made for surgical reduction in tumour mass in a palliative intention. Since a huge gastric tumour was discovered during surgery, a partial gastrectomy in combination with hemihepatectomy, splenectomy and left sided pancreatectomy was performed.

Histologically all resected organs showed metastases, the lymph nodes were free of malignant cells, resulting in a pT3, pN0, M1, R2, G1-state. After surgery, no further hypoglycemias were observed.

In a follow up examination three months later, the remaining hepatic filiae were progressive in size and the patient reported of reoccurring hypoglycemias and addephagia. Six cycles of chemotherapy with streptozotocine and 5-FU were conducted. Already during the first cycle, the blood glucose level stayed within normal range. Our patient returned to regular follow up examinations in our endocrinological department. The filiae remained constant in size, the Chromogranin A level dropped below 1000 ug/l.

Two years later the hypoglycemias reoccured, the filiae increased in size and the Chromogranin A levels rose. Having already "utilized up" chemotherapy and surgical options, the decision was made for a transarterial chemoembolization (TACE) using Epirubicine. After treatment of lesions in hepatic segments 6 and 7, the hypoglycemias vanished for about 3 months (Figure 2A, B). The patient and the family underwent counselling for the self-injection of glucagon.

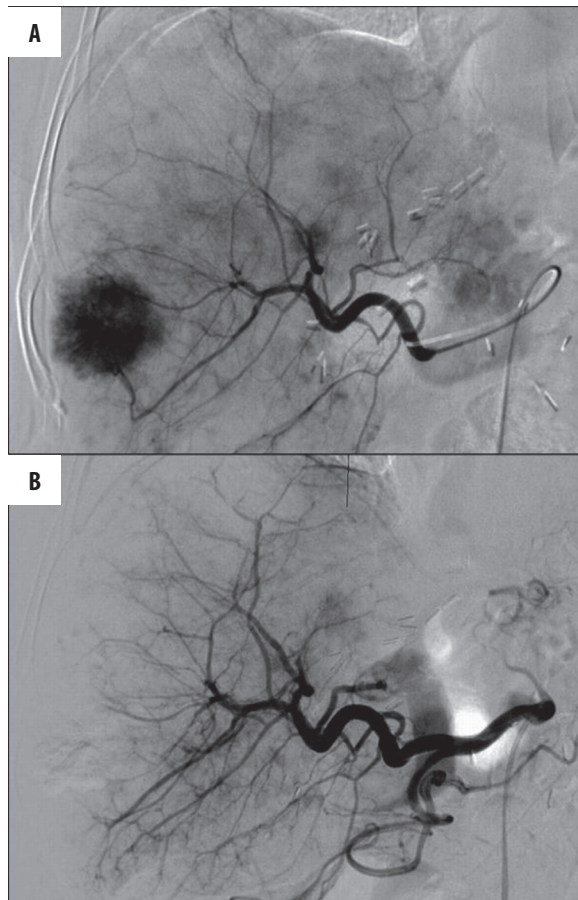


Figure 2. Angiography before (A) and after (B) TACE: Liver metastasis in segment VI.

After reoccurrence of hypoglycemias, another chemoembolization of a lesion in segment 6 was conducted. The remaining vital parts in segment 7 were also treated during this session. After a third TACE of a filia in segment 4 one week later, the patient was symptom free. The embolisations were well tolerated. No complications occurred during and after the embolisations. Presently 18 months after the last intervention she didn't suffer of any hypoglycemias or any other symptoms.

DISCUSSION

With a typical clinical picture and biochemical proof, the diagnosis of pancreatic insulinoma could be rapidly confirmed in the patient.

The detection of insulinomas is challenging, since the tumors are often smaller than 2 cm in diameter, complicating visualization. Endosonography has the highest sensitivity with 63–95%. Sensitivity rates of CT and MRI are disappointing with 40% [3]. Further clarification can be achieved in using a PET with Fluor-18-L-Dihydroxyphenylalanine (^{18}F -Dopa). This technique shows a higher sensitivity than CT and MRI and can visualize tumors undetected with other radiological techniques [4]. In case of a lacking detection of the tumor and a strong suspicion of an insulinoma due to a positive fasting test an explorative laparotomy with manual pancreatic palpation and an intraoperative ultrasound can

be conducted. Sensitivity hereby lies by roughly 97% [5]. A further diagnostic tool is somatostatin receptor scintigraphy. Here positivity for receptors also offers a therapeutic option in some cases.

In our patient, R0 resection could not be achieved due to organ infiltration and chemotherapy was added. As to be expected in malignant disease, the patient had a relapse of the hypoglycemias and the remaining metastases increased in size. The following therapeutic regimens based on local tumor control exist:

Local treatment regimens are the transarterial hepatic chemoperfusion/-embolisation with an intraarterial application of streptozotocine and Contour[®] particles or polyacryl microspheres (Embospheres[®], BioSphere Medical, Rockland, Massachusetts, USA). Another transarterial technique is the internal application of radiotherapy using Yttrium 90. A further option is the local tumor ablation using radio frequency ablation (RFA/RITA), cryoablation or the instillation of ethanol.

Ethanol injection carries the advantage of causing less collateral injury and can therefore be used in close proximity of large vessels, the bile duct or the hepatic flexure of the colon. However, the treatment requires more sessions and has a higher rate of recurrence than RF ablation of which it has been replaced in the past [6].

In RFA, a probe is inserted into the intra hepatic tumor, causing a thermal destruction based on locally administered radiofrequency. Several studies in selected patients with neuroendocrine metastasis showed an alleviation of symptoms in 69–80%, resulting in a symptom free interval of 10 months (range 10–24 months), and a mean survival period of 1.6 years [7,8]. A limitation of this treatment is that full necrosis of the tumor is achieved under 3 cm of diameter and drops dramatically by increasing size of the metastases.

Another thermal approach is cryoablation. A cryoprobe inserted in the tissue causes freeze/thaw cycles, destroying the tumor due to the formation of intra- and extracellular ice formations [9]. Since this method carries a higher risk in the treatment of greater liver tumors and the diameter of the probe is larger than in other local procedures causing a higher rate of hemorrhage it is not commonly used.

A growing interest in local treatment options lies in the use of selective internal radiation therapy (SIRT) using yttrium-90 (^{90}Y). ^{90}Y is high energy β -emitter with a mean tissue penetrance of 2.5 mm. This is attached to microspheres measuring 20–40 μm in size. Due to the local application, a radiation dose of up to 1000 Gy can be administered to the tumor, causing local destruction. As this is a relatively new method only few studies exist, showing a 1 year stable disease in 60–67% and a primary relief in symptoms in roughly 80% of patients. In those studies, especially patients with large volume tumors were included [10]. However, to clarify the value of these regimens in the treatment of hepatic metastases, further investigation is warranted.

The method based on the most experience so far is the transarterial chemoembolization (TACE), since neuroendocrine metastases are frequently hypervascularized. Streptozotocine

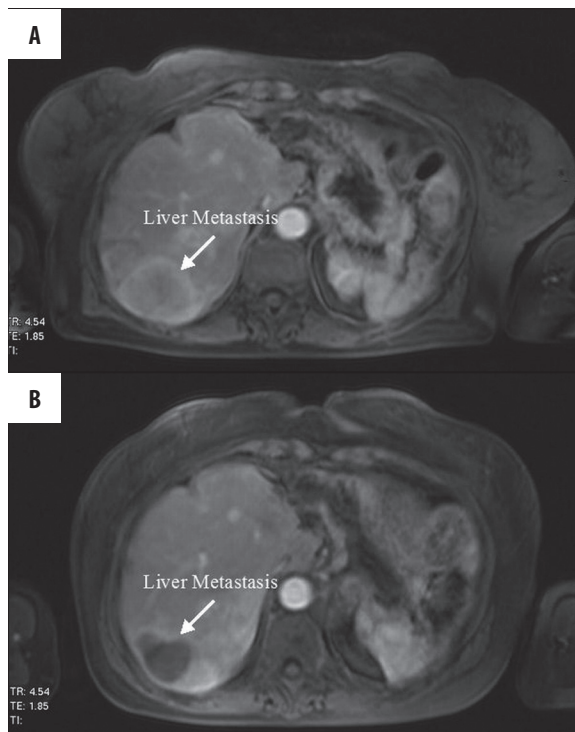


Figure 3. Liver Metastasis in segment VII before (A) and after (B) TACE.

and polyacryl microspheres (Embospheres®) are intraarterially embedded. The effect is based upon a discontinuity of the blood supply caused by the microspheres. This results in an ischaemia of the organic tissue with an increase in mitotic cells. Those show a higher sensitivity to the instilled chemotherapeutic agent [11]. Furthermore the slower wash out leads to a higher chemotherapeutic concentration in the targeted area with fewer systemic side effects. Compared to the i.v. application, local concentrations are 20 fold increased [12].

All local methods cause similar side effects. Due to the tissue necrosis, local abscesses can occur. A further complication is acute liver failure. In all studies mentioned above, those side effects occurred in up to 5% of patients. Specific systemic complications can occur in TACE and SIRT by leakage of the applied agent into the venous blood system with systemic dissemination.

To our knowledge, comparative studies of the different local methods are not available. Even specialized centers are mostly unable, to offer all a.m. therapies. Due to the good vascularization 3 chemoembolizations were conducted so far, treating the four largest hepatic metastases. In control imaging those lesions did not show any more vitality. (Figures 3B, 3B) After the first treatment she did not suffer of any more hypoglycemias for 3 months. With recurring hypoglycemias we conducted 2 consecutive chemoembolizations within one week. In follow up examinations the patient reported of not having any clinical symptoms yet. For each intervention our patients spent just two nights in the clinic. She tolerated the treatments well, not suffering of any side effects of the chemoembolizations. This therapeutic regimen holds the potential to be continued in case of need.

Due to the small number of metastatic insulinomas, no controlled studies of the therapeutic effect of the above mentioned interventions exist for this specific tumor. In a recent study comparing transarterial chemoembolization *versus* transarterial embolisation alone a prolonged survival (31.5 months to 18.2 months) and an improved response rate (50% to 25%) was demonstrated [13]. As in our case, most of the patients had already undergone chemotherapy before, however only in 1/3 of the patients have had a previous surgical tumor mass reduction in this study.

CONCLUSIONS

The patient had extended disease at the time point of diagnosis. Although life expectancy is better in a well differentiated insulinoma as in this very case, our patient is presumably still alive three years after diagnosis due to the multimodal therapeutic interventions conducted so far with very few limitations caused by the malignant insulinoma, a tumor with a 5 year life expectancy of about 44% [14]. However, the live expectancy in extended disease is typically much lower, since this study did also include cases with. According to a database of the University of Duesseldorf, the mean survival in patients with metastatic insulinoma was 2.6a [15].

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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