

Case Series

Insulinoma in the Elderly: A Report of Three Cases and Review Literature

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Abstract

Insulinoma are rare pancreatic islet cell tumors with fasting hypoglycemia due to excessive insulin secretion as the main clinical expression. The treatment of choice is surgery. In the elderly, diagnosis and treatment can be challenging. The elevated perioperative risks in this population often lead to forsake the option of surgery. Nutritional approaches and medical treatment are then often preferred. However they are not always sufficient in controlling the symptoms of hypoglycemia. In these patients other treatment options such as radiofrequency ablation and embolization are considered, although only limited data are available on the use of these strategies in this specific indication and population.

We report three cases of insulinoma in elderly patients for which different treatment options were explored.

CASE PRESENTATION

Case 1

A 82-year-old female patient with a history of metastatic insulinoma as part of multiple endocrine neoplasia type 1 (MEN-1) syndrome was admitted with recurrent falls and documented hypoglycemia.

In her medical history a resection of 3 parathyroid glands in 1985 is mentioned. In 1981 she was diagnosed with an insulinoma and underwent pancreatectomy. A partial hepatectomy was performed in 1993 for the treatment of one hepatic metastasis. Furthermore she is known with a non-producing pituitary microadenoma and in 2010 she received radioactive iodine for a toxic multinodular goiter.

In 2004 she was treated with percutaneous radiofrequency ablation (RFA) for 2 symptomatic hepatic metastases and remained symptom free until 2006, when magnetic resonance imaging (MRI) of the liver confirmed disease recurrence with 4 active metastases. A second RFA session on three percutaneous reachable lesions was successfully performed. Progression of the residual active lesion was noticed with recurrent hypoglycemia in 2010. She underwent selective angiographic embolization of the residual metastasis with complete remission of symptoms.

In 2011 the patient was readmitted with recurrent falls. A new MRI showed progression of the 3 previously ablated metastasis

without any new lesions. A second ablation of the largest metastatic lesion (4cm) was performed, but gave only limited result in glyceic control. Subcutaneous injection of octreotide 0,1mg twice a day resulted in an improvement of hypoglycemic symptoms. Short-acting octreotide was switched to long-acting lanreotide 120mg every 4 weeks. Patient was discharged to a nursing home. One year later, invalidating hypoglycemic events were noticed due to hepatic disease progression. Treatment with octreotide was stopped and changed to diazoxide 100mg three times a day with resolution of symptoms. Unfortunately, due to severe fluid retention with heart failure, treatment with diazoxide was no longer advised. After multidisciplinary oncologic conference, a new radioactive ablation of 2 large hepatic metastases was performed with improvement of hypoglycemic events. However, severe nightly events occurred. A percutaneous endoscopic gastrostomy to provide feeding during the night was eventually necessary.

Case 2

In 2006, an 84-year-old male patient was admitted because of documented clinical hypoglycemic events characterized by dysarthria and blurred vision. Medical history revealed a benign hypertrophy of the prostate and atrial fibrillation.

A starvation test confirmed hypoglycemia after 6 hours. The presence of a 1cm large neuroendocrine tumor in the pancreatic tail was diagnosed with MRI. No other pancreatic or liver lesions

were demonstrated. Pancreatectomy was advised but refused by the patient. Resolution of symptoms was obtained after dietary changes; frequent small carbohydrate rich meals during the day, before bedtime and at night.

In 2012 he was readmitted with frequent hypoglycemic events resulting in confusion and agitation, despite continuous high concentration intravenous glucose. Subcutaneous octreotide 0,1mg three times daily was associated to the treatment. A new spiral computerized tomography (CT) scan showed progression of the insulinoma (2,2cm) without metastatic lesions. The patient remained in constant need of intravenous glucose during the night to avoid serious hypoglycemia. After a multidisciplinary oncologic meeting and obtaining consent of the patient and his family, selective embolization of the insulinoma was tried.

However, due to poor visibility of the artery during angiography and the patient's agitation, the procedure could not be finished. Despite dietary adjustments, dose elevation of octreotide to three times 0,2mg a day and intravenous glucose 20% during the night, persistent hypoglycemic events made discharge to a nursing home impossible. Percutaneous endoscopic gastrostomy was refused by the patient.

During his stay he developed aspiration pneumonia with evolution to septic shock. Because of his age, his poor general condition and his primary disease, palliation was started in agreement with his family. He died a few days later.

Case 3

A 90-year-old male patient known with an insulinoma was followed in the out-patient clinic since 2005 (85 year at diagnosis). His medical records showed prostatic hypertrophy and gonarthrosis. In 2009 he successfully underwent a right hemicolectomy for an adenocarcinoma of the colon. He presented initially in 2005 with periodic episodes of confusion, blurred vision and tremor. A 72-h starvation test showed hypoglycemia with high serum insulin levels after only 5 hours. A MRI scan showed a hypervascular tumor of 4 cm, suggestive for insulinoma, located in the pancreatic head. Because of his age at time of diagnosis, the patient was treated with nutritional support. Glucose self-monitoring was advised. These measures resulted in an important reduction in hypoglycemic events. In the following years his condition was stable. A new MRI scan in 2007 showed no progression of the insulinoma.

In 2009 he was admitted after a seizure due to severe hypoglycemia. Because of the recurrence of hypoglycemic events despite appropriate dietary measures, treatment with octreotide 0,1mg three times a day was started, leading to an improvement of the situation. He could be discharged with subcutaneous lanreotide 120mg every four weeks.

End of 2012, he was in stable condition without severe hypoglycemic events.

DISCUSSION

Hypoglycemia is defined by Whipple's criteria consisting of central nervous system symptoms of neuroglycopenia, a simultaneous low blood glucose level and relief of these symptoms by administration of glucose [1].

Drugs are the most common cause of hypoglycemia in adults (mainly insulin and insulin secretagogues) [1] and elderly patients are the most vulnerable for this complication.

In adults with diabetes, mean age was 77.8 years at hospital admission for severe hypoglycemia [2]. Mainly cognitive impairment, malnutrition, polypharmacy, and a recent hospitalization are risk factors for severe hypoglycemia in older diabetic patients [3].

Non-pharmacological causes of hypoglycemia include critical illness, liver disease, renal insufficiency, alcohol, endocrine deficiency disorders, starvation and idiopathic hypoglycemia [1].

Furthermore, hypoglycemia due to hyperinsulinism is found in patients with insulinoma, insular hyperplasia, insulin autoimmune hypoglycemia and IGF-II secreting neoplasms [1].

In the geriatric population, hypoglycemic events are rather common in non-diabetic patients, mainly caused by malnutrition, non-pancreatic neoplasms and renal disease [4].

Insulinoma are rare pancreatic islet cell tumors but of all neuroendocrine tumors of the pancreas, they are the most common. In 90% of the cases, these tumors are benign. They are equally distributed among the head, body and tail of the pancreas [5].

The malignant variant often presents as larger or metastasizing tumors with lymph node or liver metastasis [5].

Insulinoma cause fasting hypoglycemia due to excessive insulin secretion, but postprandial hypoglycemia may also occur. In less than 10% they are multiple and associated with MEN-1 syndrome [1,5].

Insulinoma typically present with neuroglycopenic symptoms including headache, confusion, slurred speech and vision, behavior aberrations, lack of concentration, seizures and coma. Symptoms are often accompanied by an adrenergic response resulting in onset of hunger, diaphoresis, weakness, palpitations and nervousness [1]. Elderly patients are often lacking the adrenergic response due to autonomic dysfunction and the use of beta blockers. They will then only manifest neuroglycopenic symptoms at low glucose levels [4]. Hypoglycemia should be considered in every elderly patient with alterations in consciousness, even when they are not treated with hypoglycemic agents [4].

Differential diagnosis should be made with cerebrovascular insult, dementia, epilepsy, arrhythmia, electrolyte disturbances and infectious disease.

Diagnosis

The key feature in the diagnosis of insulinoma is endogenous hyperinsulinism. Critical biochemical findings are plasma insulin concentrations of at least 3 μ U/ml (18 pmol/l), c-peptide concentrations of at least 0,6 ng/ml (0,2 nmol/l) and proinsulin concentrations of at least 5 pmol/l when the fasting glucose concentrations are below 55 mg/dl without detectable oral hypoglycemic agents levels and no circulating insulin antibodies. Beta- hydroxybutyrate levels of 2.7 mmol/liter or less and an increase of plasma glucose of at least 25 mg/dl after IV glucagon provide evidence of insulin excess [1].

The diagnosis of an insulinoma is best made by a 72-h starvation test; 65% of the patients fulfill the diagnostic criteria in less than 24 hours [1,6]. After acquiring clinical and biochemical evidence for underlying insulinoma, noninvasive procedures to localize the tumor should be used; spiral CT, MRI and trans abdominal ultrasonography [7]. Negative imaging does not exclude the diagnosis because most of the tumors are small (less than 1cm) [1,5].

Other investigations to localize the tumor are somatostatin receptor scintigraphy, endoscopic pancreatic ultrasound and selective angiogram with calcium stimulation [5,7].

Most insulinoma are diagnosed before surgery. Intraoperative pancreatic ultrasound is used for localization of tumors during surgery [5,8].

Therapy

Surgical removal through enucleation or segmental resection is the treatment of choice. The goal is to remove the tumor while preserving as much as normal pancreas [5].

Enucleation is reserved for small (< 2cm), benign insulinoma with a minimum distance of 2-3mm to the main pancreatic duct [9]. It should only be undertaken for tumors without evidence for malignancy. In patients with MEN-1, partial resection is normally preferred [5]. Surgery may be curative in 75% to 98% of patients [9].

For malignant tumors with metastatic disease, reduction of the tumor mass has been reported to be beneficial. Prolonged survival is often possible given the slow-growing nature and symptom control can be achieved [10].

Surgery can be performed via laparoscopy; however conversion to open exploration is necessary in up to 44% of the cases [11].

Postoperative complications include pancreatitis, pancreatic pseudocysts, pancreatic leaks and fistula. Operative mortality occurs in up to 3.7% and major postoperative morbidity in up to 33% of patients [12].

When metastatic disease of the liver is present, surgical resection in selected patients remains the treatment of choice for curative and palliative intent. However hepatic resection for cure is possible in less than 10% of affected patients. In the absence of curative intent, alternate therapies should be explored [5].

Medical treatment with diazoxide, octreotide or verapamil can be used in patients who are not good candidates for surgery, with metastatic disease or who refuses surgery [5,10]. Angiographic embolization and radiofrequency ablation are alternatives if symptom control is not achieved with conservative treatment alone.

Diazoxide is a potassium channel activator which causes vasodilation and reduces insulin secretion in pancreatic islet cells. A response rate up to 70% has been reported when used in the treatment of hypoglycemia caused by hyperinsulinism [13]. Side effects such as fluid retention and rash are common (up to 50% of the patients) but mostly not troublesome [13]. In some countries diazoxide is not available for prescription. It has

been used successfully in a 95-year-old patient with insulinoma without severe side effects [14]. However in our patient, the treatment was poorly tolerated with severe fluid retention.

Calcium-channel blockers have successfully been used for the treatment of hypoglycemia caused by nesidioblastosis and insulinoma [15,16,17]. They inhibit the glucose-induced insulin release by pancreatic B-cell. Isolated cases were reported in elderly patients with insulinoma; a 94-year-old woman who refused surgery was treated successfully with verapamil only [18]. An 80-year-old woman was free of symptoms with the combination therapy of amlodipine and verapamil [19].

Octreotide binds with high affinity to the somatostatin receptor (SSTR) subtypes 2 and 5 [20] and has inhibitory effects on insulin secretion. These receptors are expressed on neuroendocrine tumors. Octreotide is used in the treatment of insulinoma with a response rate around 50% [21]. In some circumstances it may further aggravate hypoglycemia by the suppression of glucagon secretion [22]. Other possible side effects are diarrhea, abdominal pain and cholelithiasis. The initial dosage is usually 50 to 100µg administered twice or three times daily subcutaneously with upward titration. To improve patients' comfort, a switch to long-acting octeotide (20 to 30mg intramuscularly at 4-week intervals) or lanreotide autogel (60mg, 90mg or 120mg given at 4-week intervals subcutaneously) can be considered. Daily octreotide injections should be continued for at least 2 weeks after the initial injection of the long-acting octreotide, the time needed to reach therapeutic levels [5].

Literature study showed 3 cases of successful treatment of hypoglycemia with octreotide alone in elderly patients with insulinoma [23,24]. A good response was also obtained in our patient who has been treated with octreotide for several years without side effects.

Embolization is an effective and popular therapy for certain tumors, but its use in insulinoma is still based on empiric knowledge [25,26]. Islet cells are surrounded by a rich blood supply which makes them possible candidates for therapeutic embolization. The therapeutic success is dependent on the extent of tumor necrosis achieved and the experience of the interventional radiologist [26]. Successful embolization of insulinoma has been described in only a few cases [25,26,27] emphasizing the limited experience with this procedure. It is an invasive procedure and pancreatitis is a common complication [26]. It has been used in an 84-year-old woman with an insulinoma who refused surgery. Mild pancreatitis was present for a few days after the procedure. She was free of symptoms 1 year after the procedure [27]. In one of our cases embolization of the insulinoma was considered as treatment option. However due to poor visibility and the agitation of the patient, the procedure could not be performed.

Hepatic artery embolization has been used to treat patients with liver metastasis to achieve symptom control. The blood supply to hypervascular tumors is derived from the hepatic artery whereas normal hepatic tissue is supplied by the portal venous system [5]. Possible complications are pain, fever, infection and bleeding [5]. It has been used for the treatment of liver metastasis from neuroendocrine tumors with a response rate varying from

Table 1: Overview of non-surgical treatment for insulinoma, reported cases in geriatric population.

| Patient | Age | Gender | Treatment | Side effects | Outcome |
|------------------|-----|--------|---|---|--|
| 1 ¹⁴ | 95 | F | Diazoxide | - | Good response |
| 2 ¹⁸ | 94 | F | Verapamil | - | Good response |
| 3 ¹⁹ | 80 | F | Verapamil + Amlodipine | - | Good response |
| 4 ²³ | 76 | F | Octreotide | Gallstone | Symptom free for at least 1 year |
| 5 ²³ | 85 | F | Octreotide | - | Symptom free for at least 3 years |
| 6 ²⁴ | 83 | F | Octreotide | - | Symptom free for at least 33 months |
| 7 ²⁷ | 84 | F | Embolization | Mild pancreatitis | Symptom free for at least 1 year |
| 8 ³⁵ | 80 | F | RFA of pancreatic insulinoma | - | Symptom free for at least 7 months |
| 9 ³⁷ | 78 | F | Ethanol ablation | Mild pancreatitis | Symptom free for at least 34 months |
| 10 ³⁸ | 78 | F | Ethanol ablation | Asymptomatic pancreatitis hematoma and ulceration of the duodenal wall | Symptom free for at least 2 years |
| 11 ³⁹ | 82 | M | Ethanol ablation (2 sessions) | - | Symptom free for at least 13 months under low dose diazoxide |
| 12 ³⁹ | 80 | F | Ethanol ablation (2 sessions) | - | Symptom free for a least 12 months |
| 13 ³⁹ | 79 | F | Ethanol ablation | Pancreatitis with pseudocyst | Symptom free for at least 7 months |
| 14 | 82 | F | Repeated RFA of hepatic metastasis Hepatic embolization Octreotide Diazoxide | - - - Severe fluid retention | Symptom free for several years Symptom free for 1 year Recurrence after 1 year STOP treatment due to side effects |
| 15 | 90 | M | Diet intervention Octreotide Embolization | - - | Good response for 6 years Partial response Not possible because of poor visibility |
| 16 | 90 | M | Diet intervention Octreotide | - - | Good response for 4 years Good response since 2009 |

33 to 80% [28,29]. In our first case, this treatment option was successfully performed, with achievement of symptom control without severe complications for a 1 year period.

Percutaneous radiofrequency ablation (RFA) is known as a minimally invasive procedure to treat primary liver tumors and hepatic metastasis [30]. It has been used safely in patients aged 75 and older without an increased risk for severe complications [31]. It is also a reasonable option for the treatment of unresectable metastasis of neuroendocrine tumors [32,33]. It has a lower morbidity than embolization which makes repeated therapeutic sessions possible [34]. The procedure was repeatedly used in our first case, was uncomplicated and resulted in good symptom relieve.

Limited data is reported about RFA of insulinoma located in the pancreas and only a few cases have been described [35,36]. It harbors the risk of pancreatitis and thermal injury of close anatomic structures; duodenum, common bile duct, transverse colon, portal vein, mesenterial vessels or stomach. Thermal injury of the pancreatic duct increases the risk of pancreatic leakage and fistula [35,36]. General anaesthesia is mostly required and it is only useful in small lesions. Long-term efficacy is uncertain. It has successfully been performed in an elderly patient with insulinoma who refused surgery. There were no RFA-related complications and there was a good clinical response [35].

Endoscopic ultrasound- guided ethanol ablation of insulinoma is new alternative treatment option. It was reported

for the first time in 2006 in a 78-year-old patient [37]. Ethanol 95% was injected directly into the lesion using echo-endoscopy with complete tumor remission. After the procedure the patient developed a mild pancreatitis and remained symptom free for at least 34 months. Furthermore, this new technique has been performed successfully in 4 other geriatric patients [38,39]. It appears to be a safe and efficient alternative, but the clinical experience is limited.

CONCLUSION

With these 3 cases we emphasize the difficulties we are facing when diagnosing and treating elderly patients with an insulinoma. Literature studies show isolated case reports of elderly patients with insulinoma presenting with different signs and symptoms. It is a rare condition and the differential diagnosis is challenging, especially in elderly patients without the classical adrenergic hypoglycemic symptoms. General frailty in this elderly population hinders invasive investigations and treatment. Surgery remains the treatment of choice. However due to the increased risks in this population, this option is often forsaken and other possibilities need to be explored. Medical treatment and dietary changes are preferred.

Angiographic embolization and radiofrequency ablation are alternatives if symptom control is not achieved with conservative treatment alone. However, only limited data on outcome and/or side effects are available (Table 1).

The different therapeutic options were used in our three cases with variable success.

The 3 cases show the different nature of insulinoma, from a disease which can be controlled by conservative measures to an invasive and rapidly invalidating disorder. The invalidating evolution of this disease urges to search for new noninvasive diagnostic and therapeutic options, especially in this elderly population. More data of noninvasive therapeutic strategies, their management, complications and outcome, could help other clinicians to make therapeutic choices in the elderly.

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