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MINI REVIEW

Ovarian tumors secreting insulin

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Abstract Combined ovarian germ cell and neuroendocrine tumors are rare. Only few cases of hyperinsulinism due to ovarian ectopic secretion have been hypothesized in the literature. An ovarian tumor was diagnosed in a 76-year-old woman, referred to our department for recurrent hypoglycemia with hyperinsulinism. In vivo tests, in particular fasting test, rapid calcium infusion test, and Octreotide test were performed. Ectopic hyperinsulinemic hypoglycemia was demonstrated in vivo and hypoglycemia disappeared after hysteroadnexectomy. Histological exam revealed an ovarian germ cell tumor with neuroendocrine and Yolk sac differentiation, while immunostaining showed insulin positivity in neuroendocrine cells. A cell culture was obtained by tumoral cells, testing Everolimus, and Pasireotide. Insulin was detected in cell culture medium and Everolimus and Pasireotide demonstrated their potentiality in reducing insulin secretion, more than controlling cell viability. Nine cases of hyperinsulinism due to ovarian ectopic secretion reported in literature have been reviewed. These data confirm the ovarian tissue potentiality to induce hyperinsulinemic hypoglycemic syndrome after neoplastic transformation.

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Introduction

Malignant germ cell tumors of the ovary are a heterogeneous group of tumors accounting 2–5 % of all ovarian tumors. Neuroendocrine differentiation in a germ cell tumor is extremely rare and is usually represented as a monodermal teratoma. One third of insular carcinoids of the ovary have been associated with the carcinoid syndrome despite the absence of metastases [1].

The clinical syndromes arising from ectopic hormone production and in particular ovarian ectopic hormone secretion are uncommon. The most common functional ovarian tumor manifestations are hyperandrogenism and hyperestrogenism. Human chorionic gonadotropin (HCG)-related endocrine disorders are common too, while hyperthyroidism, carcinoid syndrome, non-endocrine paraneoplastic syndrome, Cushing syndrome, and hypoglycemia are extremely rare [2].

Hypoglycemia is defined as symptomatic when associated with the typical Whipple triad (i.e., symptoms of hypoglycemia, low serum glucose, and symptoms relief by glucose intake). The most frequent cause of spontaneous hyperinsulinemic hypoglycemia is a pancreatic insulinoma, an insulin secreting neuroendocrine tumor. Insulinomas are usually located in the pancreas, while extrapancreatic insulinomas are rare (0.5 % of cases) and they are usually located in peripancreatic bed.

Only scattered cases of hypoglycemia due to ectopic ovarian insulin production have been hypothesized in literature, the last one in 2007. Here, we report the case of a 76-year-old woman which was referred for continuous

hyperinsulinemic hypoglycemia and provide the first evidence in vitro of insulin secretion by the ovarian neuroendocrine tumor.

Our experience

Case report

A 76-year-old woman was admitted to our department for recurrent hot flushes, sweating, and dizziness always associated to fasting hypoglycemia. Her medical history was relevant for type 2 diabetes mellitus previously pharmacologically treated, hypertension, and atrial fibrillation. Physical examination was remarkable for abdominal obesity and ascites, no signs of hyperandrogenism. Tumor markers and hormonal assessment, performed at the Central Laboratory of Padova Hospital with standard methods, are summarized in Table 1. Hypoglycemia was remarkable and the patient needed continuous i.v. glucose administration. The fasting test was stopped at the fifth hour due to heavy symptoms of neuroglycopenia. Blood samples were collected and hypoglycemia was demonstrated; in addition, insulinemia was inappropriately elevated, as for C-peptide levels. Suspecting an insulinoma, abdominal US was performed, showing a spiculated not homogeneous mass of 10 cm in diameter in the left adnexal region. Abdominal CT confirmed the presence of a necrotic-colliquative expansive lesion in left adnexal, cranially in contact with uterine fundus, described ascites while no mass was detected in the pancreatic region. The positivity of ^{18}FDG PET-CT was coherent with the suspect of malignancy, describing multiple broad areas of intense uptake (SUV-max 22) in left adnexal (Fig. 1). Octreoscan® was negative for pathological uptake. The preoperative cytological study of the ascitic fluid was negative for neoplastic cells. One month after the admission the patient underwent hysteroadnexectomy and she died 8 days later due to septic complications from a gallbladder empyema, discovered during surgery. Autopsy was not performed. Before hysteroadnexectomy hypoglycemia was registered also during total parenteral nutrition, while after surgery glucose levels remained above the upper limit, requiring insulin infusion therapy.

Informed consent was obtained by patient's guardian for publication of submitted article and accompanying images.

Dynamic tests

Fasting test was performed measuring blood glucose, insulin, and C-peptide hourly after the last meal because of the high frequency of hypoglycemic events recorded during hospitalization. The patient showed symptoms and signs of hypoglycemia associated with inappropriate high levels of insulin and normal levels of C-peptide. This pathological trend was observed since the third point of the curve, taken at the third hour, while symptoms occurred at the fifth hour (Fig. 2a).

We performed the rapid calcium infusion test with infusion of calcium gluconate 2.5 g in 90 s and measurement of blood glucose, C-peptide, and insulin levels at time 0′–2′–5′–10′–15′–30′. It did not elicit any peak of insulin secretion neither in the second or fifth minute, as represented in Fig. 2b.

Regarding the Octreotide test, 100 μg Octreotide was administered s.c. and blood samples were collected hourly over 6 h to measure blood glucose, serum insulin, and C-peptide. We observed an early suppression of insulin secretion; however, at the fourth hour both symptomatic

Table 1 Baseline endocrine evaluation

Test	Value	Normal range
Serum cortisol (8 a.m.)	433 nmol/L	138–690 nmol/L
Serum cortisol (6 p.m.)	439 nmol/L[a]	69–345 nmol/L
Urinary cortisol	275 nmol/24 h	90–694 nmol/24 h
ACTH (8 a.m.)	21 ng/L	10–50 ng/L
ACTH (6 p.m.)	23 ng/L	5–25 ng/L
FT4	12.85 pmol/L	9–22 pmol/L
FT3	3 pmol/L[a]	3.9–6.8 pmol/L
TSH	1.83 mIU/L	0.2–4 mIU/L
Beta-HCG	4 U/L	0–10 U/L
NSE	4.2 μg/L	0–17 μg/L
5-HIAA	15 μmol/24 h	10–31 μmol/24 h
CA 15.3	9.2 kU/L	0–31 kU/L
Glucagon	87 ng/L	50–150 ng/L
LH	0.1 U/L[a]	11–61.5 U/L
FSH	0.4 U/L[a]	35–150 U/L
Serotonin	0.32 μmol/L	0.28–1.7 μmol/L
Calcitonin	33.4 ng/L[a]	0–20 ng/L
Chromogranin A	502 μg/L[a]	0–98 ug/L
CA 125	827.2 kU/L[a]	0–35 kU/L
CA 19.9	245.3 kU/L[a]	0–37 kU/L
Free testosterone	312 pmol/L[a]	1–6 pmol/L
Testosterone	52.05 nmol/L[a]	0.35–3.12 nmol/L
SHBG	60 nmol/L	18–114 nmol/L
DHT	6.7 nmol/L[a]	0.03–0.62 nmol/L
DHEAS	0.8 μmol/L[a]	0.9–11.7 μmol/L
17-OH progesterone	45.1 nmol/L[a]	0.3–1.5 nmol/L
Progesterone	5.8 nmol/L[a]	0.3–2.3 nmol/L
17-beta-estradiol	1526 pmol/L[a]	<150 pmol/L
AFP	218.8 μg/L[a]	0–7 μg/L
CEA	7.4 μg/L[a]	0–5 μg/L

[a] Abnormal values

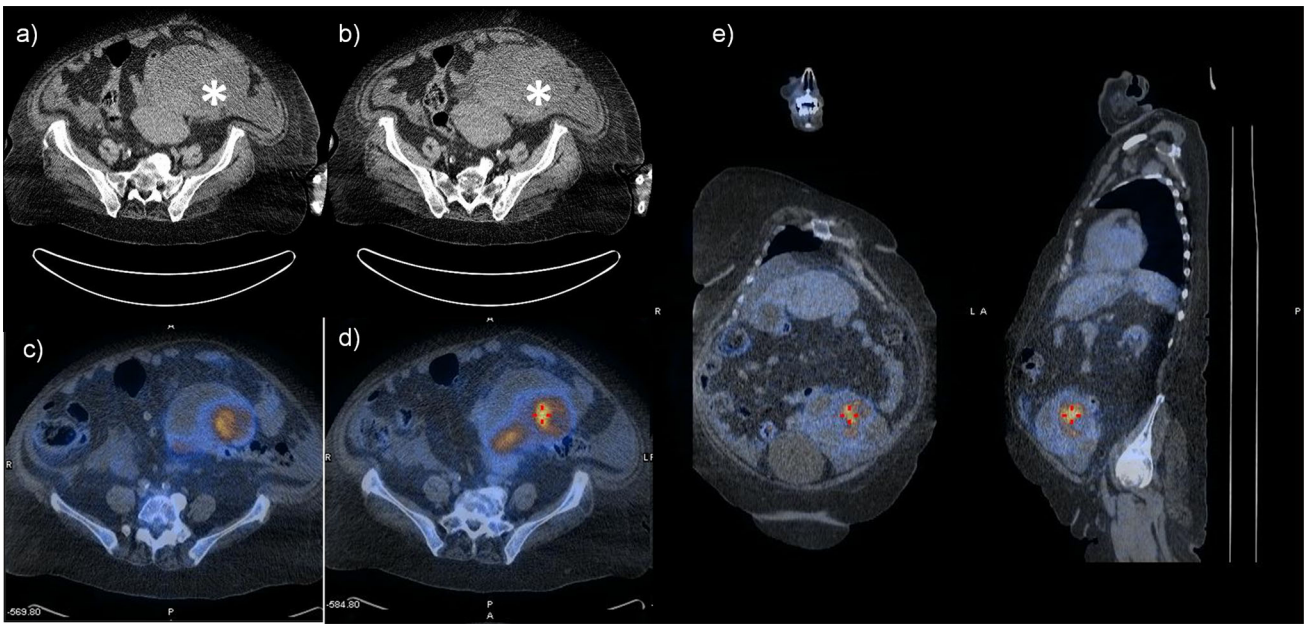

Fig. 1 Tumor imaging: CT (*a*, *b*) and 18FDG PET-CT (*c*–*e*)

hypoglycemia and hyperinsulinemia were documented. The results are summarized in Fig. 2c.

Histologic exam and immunostaining

Tissue samples were collected under sterile conditions at the time of surgery, following the guidelines of the local committee on human research. A left ovarian mass of 12 × 14 × 8.5 cm was present: mainly solid, with cystic, necrotic, and hemorrhagic areas. At histology the tumor showed areas consistent with Yolk sac tumor as well as insular carcinoid, the latter representing about 80 % of the tumor mass. It was a combined germ cell and neuroendocrine tumor which could have "dedifferentiated" to an aggressive germ cell tumor and a higher grade NET.

Immunostaining for Cytokeratins (CK7 and CK20), AFP and anti-hepatocyte was positive in the Yolk sac component, while synaptophysin, chromogranin A and insulin staining was present in the areas with neuroendocrine differentiation, confirming the morphological diagnosis (Fig. 3). Immunostaining for pancreatic polypeptide (PP) was negative. The neuroendocrine component was well-differentiated and its proliferation index (Mib-1) was variable from 20 to 72 % with a prevalent value of 40 %. In the Yolk sac the Mib-1 was lower (13 %).

According to the 2014 WHO classification of ovarian tumors [1] this case is a germ cell tumor with Yolk sac component (ICD-O code 9071/3) and Carcinoid (ICD-O code 8240/3). If referred to the 2010 WHO classification of neuroendocrine tumors [3], the neuroendocrine component should be upgraded at G3. However, it must be taken into account that this grading system is just for GEP NENs.

No evidence of tumor spread out of the ovary was reported at surgery and pathological examination of the surgical specimen confirmed a tumor limited to the ovary consistent with stage 1A (T1-N0-M0) according to the 2014 FIGO staging classification [4].

Additional immunohistochemical studies showed a GLUT4 expression, in particular in neuroendocrine well-differentiated cells, while IRS1 and GLUT1 were negative. Somatostatin receptors immunohistochemical evaluation showed only SSTR3 expression (Fig. 4) while SSTR1, 2A, and 5 were absent. Hormonal receptor for estrogen, progesterone, and androgen were all negative in the tumor. The intermixed ovarian stroma disclosed focal presence of progesterone receptor. Also rare cells Leydig-similar were present in the stroma, but wide necrosis did not allow a definite morphological and immunohistochemical identification.

Culture cell and cell viability

A portion of the fresh ovarian tumor tissue was collected under sterile conditions and treated with 100 nM Pasireotide or Everolimus, as previously described [5, 6]. We were able to detect a significant amount of insulin in the medium of the ovarian cancer cell culture (12.3 μIU/ml). Remarkably, a complete inhibition of insulin secretion was observed in vitro at maximal doses of both Pasireotide and Everolimus with no effect on cell viability (Fig. 5).

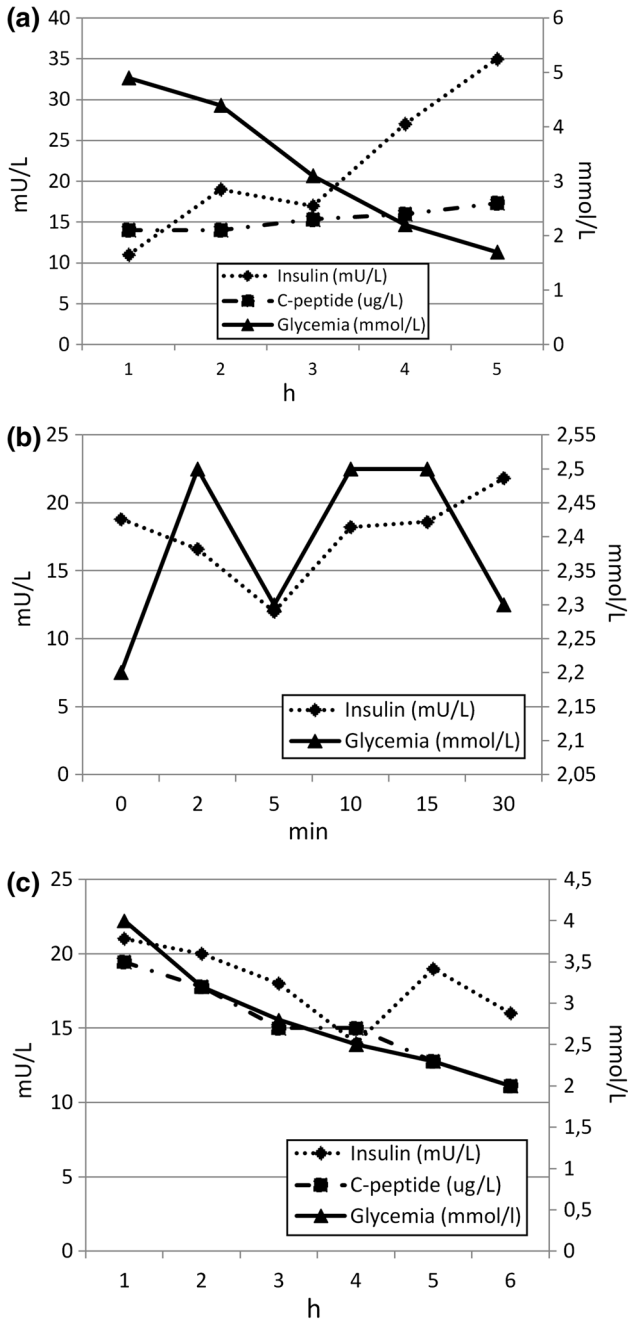

Fig. 2 **a** Fasting test. On the *left* ordinate insulin scale, on the *right* C-peptide, and glycemia scale. On the *x axis* time of blood tests, performed hourly since the beginning of the test; **b** rapid calcium infusion test. On the *left* ordinate insulin scale, on the *right* glycemia scale; on the *x axis* time of blood tests after Calcium infusion. **c** 100 μg octreotide test. On the *left* ordinate insulin scale, on the *right* glycemia, and C-peptide scale. On the *x axis* time of blood test, performed hourly after the octreotide administration

Discussion

Only 9 cases of insulin production by ovarian tumors have been hypothesized but not fully confirmed in literature; they are reviewed in Table 2 [7–13].

To the best of our knowledge, this is the first study demonstrating in vivo and in vitro that the symptomatic hypoglycemia was due to insulin hypersecretion by an ovarian tumor.

The fasting test results were in agreement with endogenous hyperinsulinism according to the current guideline of the Endocrine Society for evaluation and management of adult hypoglycemic disorders [14].

The dynamic tests in vivo were consistent with hypoglycemia due to endogenous hyperinsulinism, probably not related to a pancreatic insulinoma. Since 1975 [15], it has been observed that i.v. calcium infusion provokes insulin release in patients with pancreatic beta-cell carcinoma. In 1986 Brunt et al. [16] compared long infusion toward rapid i.v. calcium infusion in the diagnostic evaluation of hyperinsulinemic hypoglycemia, finding a better performance by the rapid infusion test in detecting beta-cell neoplasms. These data were confirmed also in our hands [17]. In this case, the absence of insulin secretion after rapid calcium infusion suggested that the pancreatic beta-cell regulatory network could not be involved in hyperinsulinism. Abdominal CT, whose sensitivity for the detection of islet-cell tumors varies from 71 to 82 % [18], did not detect any pancreatic mass, data confirmed by ^{18}FDG PET-CT and Octreoscan® with SPECT (sensitivity 87.5 %) [19]. Furthermore, the surgical procedure did not detect any sign of a pancreatic mass.

Octreotide test, proposed in 1989 by Reubi et al. [20] for prediction of therapy response in acromegaly, has been recognized to predict the clinical response to somatostatin analogs therapy also in hyperinsulinemic hypoglycemia [21]. Somatostatin analogs are rarely used for long-term therapy in patients with endogenous hyperinsulinism and only few data are present in medical literature, since surgery and diazoxide are the most effective therapies. Somatostatin analogs could worsen hypoglycemia in hyperinsulinemic hypoglycemic syndromes because of their effect on glucagon secretion. It is well known that Octreotide has a better affinity for SSTR2A and SSTR5 and the most expressed SSTR subtype on alpha cells is SSTR2A and on beta cells are SSTR1 and SSTR5 [22]. After Octreotide infusion, hypoglycemia could be related not only to an insufficient beta-cell inhibition, but also to the inhibition of glucagon release. In this case, the result of the suppressive test could be explained by insufficient or no response by the ovarian tumoral cells and by glucagon inhibition. Immunohistochemical study of somatostatin receptor subtypes on tumoral cells revealed isolated SSTR3 positivity, coherent with functional study performed by Octreoscan®, which was negative. SSTR3 expression may justify the insulin secretion response in cell culture to Pasireotide, which binds multiple somatostatin receptors. It was also demonstrated that Pasireotide has some effects on insulin secretion by acting through SSTR3 [23].

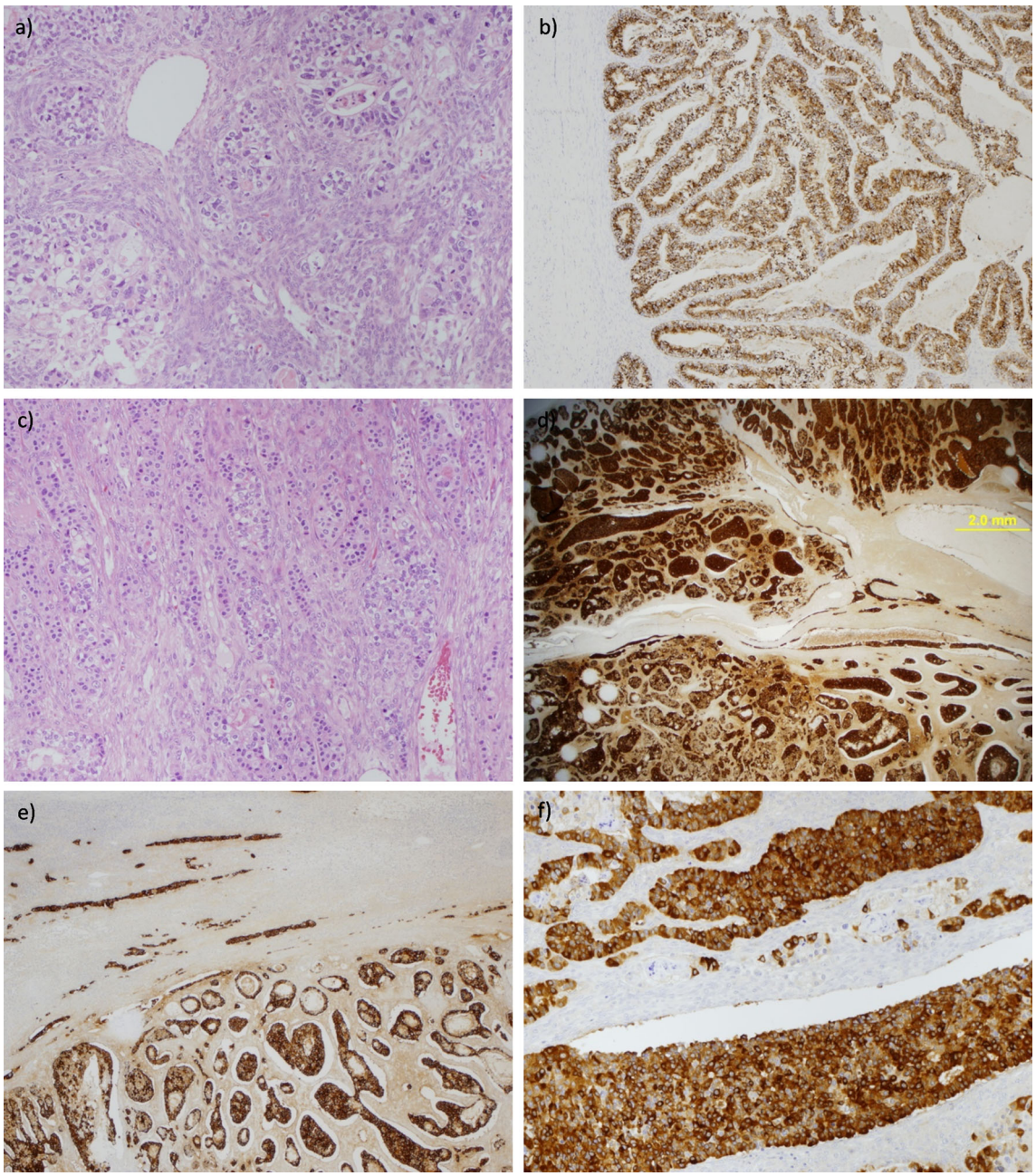

Fig. 3 **a** Yolk Sac tumor with liver-like differentiation, EE optical microscopy ×100, **b** immunostaining for anti-hepatocyte ×50, **c** neuroendocrine tumor EE ×100, **d** immunostaining for NSE ×12,5, **e** immunostaining for Chromogranin A ×25, **f** immunostaining for insulin ×100

Immunohistochemistry was able to show that neuroendocrine well-differentiated cells were positive for GLUT4, but not for other glucose transporters. In particular, the lack of GLUT1 protein appears to be in contrast with many other reports in which GLUT1 mRNA and protein were found to be expressed in primary epithelial ovarian cancer [24]. The presence of the insulin dependent glucose transporter GLUT4 was only seldom detected in ovarian cancer showing also a correlation with the severity of the disease [25]. GLUT1 has been found to be overexpressed in a variety of malignancies whereas GLUT4, which is commonly found in insulin-sensitive tissue such as cardiac, skeletal, and muscular tissue, seems to have a minor role in tumorigenesis. In the normal endocrine pancreas, which must sense and respond suitably to postprandial increases of blood glucose [26, 27], any perturbation of glucose-sensing of beta cells could lead to inappropriate insulin secretion and glucose regulation with the appearance of

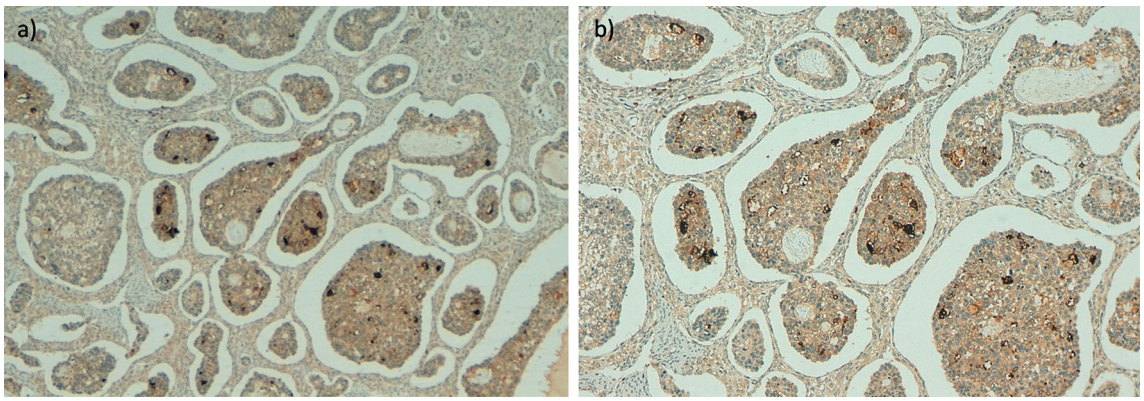

Fig. 4 Immunostaining for SSTR3, **a** ×4, **b** ×10

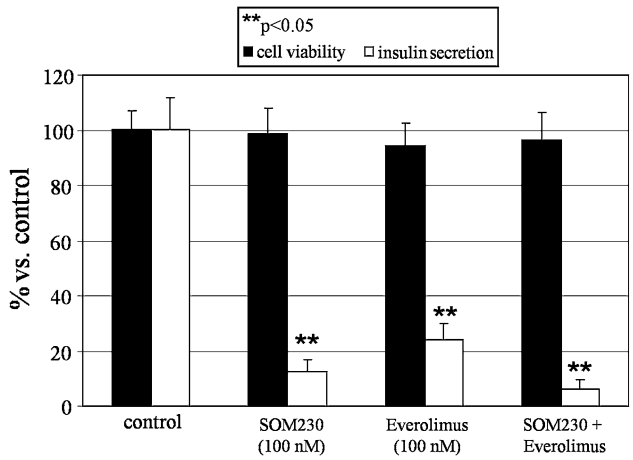

Fig. 5 Everolimus and Pasireotide effects on cell viability and insulin secretion in cell culture obtained from tumoral cells

hyper or hypoglycemia. In a similar way, disruption of the glucose sensing in ovarian cancer cells harboring the insulin secretory machine, but not an appropriate glucose insulin secretion coupling mechanism, could lead to an autonomous and dysregulated insulin secretion and to a subsequent continuous delivery of insulin with hypoglycemia. Furthermore, very surprisingly the neuroendocrine ovary cancer cells do not possess the early crucial steps of insulin signaling pathway. In fact, we observed the lack of IRS1 in these cells further suggesting the disconnection in the cause-effect relationship between the insulin action and GLUT4 activity. This particular GLUT4/GLUT1/IRS-1 pattern could be explained by the GLUT4 translocation mediated by ER-dependent PI3 K/Akt signaling by 17-beta-estradiol, described in MCF-7 cells [28].

Therapeutic options for hyperinsulinemic hypoglycemia management are represented by frequent carbohydrate-enriched meals, diazoxide and, in some cases, somatostatin analogs, and continuous i.v. glucose infusion. Recently, mTOR inhibitors have been suggested as an option for their success in controlling hypoglycemic symptoms in metastatic insulinoma [29] and in severe hyperinsulinemic hypoglycemia due to beta-cell hyperplasia [30]. Many mechanisms are suggested to be responsible for this effect, in particular promoting insulin resistance and, regarding to beta cells, inhibition of insulin secretion and apoptosis induction. To the best of our knowledge, in medical literature no data are present regarding mTOR inhibitors effect on insulin secreting tumoral cells in vitro. In our tumoral cell culture, Everolimus provoked a great reduction of insulin in the medium, while no effect was observed on cell viability. We could not establish whether this effect is related to inhibition of transcription or inhibition of secretory phase, but this observation could confirm previous data about the direct effects of mTOR inhibitors on insulin secretion and production [31] and may justify the absence of anti-tumoral action which is reported in some papers [29].

Regarding biochemical hyperandrogenism, no signs of virilization were present, neither elevated levels of hemoglobin nor hematocrit because, differently from insulin, high levels of testosterone need peripheral receptor activation to induce clinical symptoms [32]. Moreover, clinical virilization is more difficult to detect in postmenopausal woman. The increased values of testosterone have been reported in Yolk sac tumors of the ovary, along with Leydig-cells on the ovarian stroma [33]. In our case, the widespread necrosis did not allow a definite identification, but the mechanism is probably the same.

Conclusion

Although its rarity, this case confirms the ovarian tissue potentiality to induce hyperinsulinemic hypoglycemic syndrome after neoplastic transformation. Furthermore, our study suggests that pharmacological therapies, such as Everolimus and Pasireotide, may be attempted with the aim

Table 2 Summary of papers describing ovarian tumors secreting insulin

	Author, title, journal, year	Clinical data	Histological exams	Insulin immunostaining and other exams
1	Frantz et al. Tumors associated with hypoglycaemia: pancreatic and extrapancreatic, Am J Med, 1956 [7]	Ovarian tumor associated to symptomatic hypoglycemia, responsive to surgery	Granulosa cells tumor, NSILA, and insulin were not tested	Not performed
2	Srivastava, Hypoglycaemia associated with nonpancreatic mesenchymal tumors, Int Surg, 1976 [8]	Not given	Disgerminoma and ovarian cystadenoma, NSILA and insulin were not tested	Not performed
3	Stagno et al. Strumal carcinoids of the ovary. An immunohistologic and ultrastructural study, Arch Pathol Lab Med, 1987 [9]	Asymptomatic	Two ovarian carcinoids producing insulin	Positive immunostaining for insulin
4	Morgello et al. Ectopic insulin production by primary ovarian carcinoid, Cancer, 1988 [10]	Hyperinsulinemic hypoglycemic crisis for 12 years. Subtotal pancreatectomy was performed, with no effects on hypoglycemic events, so diazoxide therapy was started. She died for respiratory and metabolic acidosis	Ovarian carcinoid with small areas of mucinous cystadenoma. A parathyroid adenoma and microscopic focus of pituitary hyperplasia were found, suggesting a possible diagnosis of MEN I.	Electron microscopy: endosecretory granules, the majority with electron-dense cores with peripheral halos, and typical beta secretory granules. IHC: 5 % of cell positive cytoplasmatic staining for insulin, diffusely NSE staining positivity in cytoplasm of carcinoid tumor cells
5	Leach et al. Aberrant hormone production from ovarian neoplasms: strategies for diagnosis and therapy, World J Surg, 1990 [11]	Recurrent seizures during non-eventful pregnancy and status epilepticus associated to hypoglycemia, hyperinsulinism and high levels of C-peptide 2 weeks later	Left ovarian mass consistent with strumal carcinoid tumor	Carcinoid component contained cells with insulin immunoreactivity
6	Ashton et al. Strumal carcinoid of the ovary associated with hyperinsulinaemic hypoglycaemia and cutaneous melanosis, Histopathology, 1995 [12]	Hypoglycemic crisis initially responsive to therapy with diazoxide and associated to cutaneous melanosis	Strumal carcinoid of the right ovary, scattered foci of thyroid tissue, consisting of follicular structures lined by cuboidal epithelium and containing eosinophilic material, intermixed with carcinoid tumor with trabecular pattern and whose cells varied in shape from columnar to polygonal. The ribbons of tumor cells were separated by dense hyalinised connective tissue containing occasional small foci of calcification. Many of the cells had a columnar appearance with copious cytoplasm and red–brown granularity	Positive immunoreactivity for insulin, PP, glucagon, α-MSH, somatostatin, HCG, gastrin, TG, CgA, serotonin and calcitonin
7	Morken et al. Insulin producing primary ovarian carcinoid tumor, Acta Obstet Gyn Scan, 2007 [13]	Several episodes of confusion and amnesia	Multi-cystic tumor from the right ovary, cystic epithelial tumor with some solid infiltrative parts consistent with carcinoid tumor for a positive reactivity to neuroendocrine markers	IHC: focal positive for insulin, strongly positive for synaptophysin and more focal positive for Chromogranin A

of controlling ectopic neoplastic hyperinsulinemic syndromes.

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Conflict of interest Dr. Maffei has received unrestricted Grants from Novartis, Italfarmaco, and Ipsen and has been a member of Novartis, Italfarmaco, and Ipsen advisory boards.

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