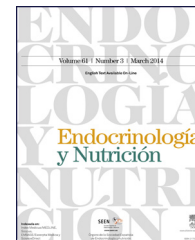


ENDOCRINOLOGÍA Y NUTRICIÓN

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SCIENTIFIC LETTERS

Diabetes, ovarian tumor, hyperparathyroidism, and papillary cancer: A chance association?☆



Diabetes, tumor ovárico, hiperparatiroidismo y cáncer papilar: ¿una asociación casual?

Endocrine tumors are a very heterogeneous group of neoplasms. Mainly neuroendocrine tumors may occur grouped into hereditary tumor syndromes which are transmitted as autosomal dominant disorders. The following syndromes are well characterized, and the genetic changes responsible for their occurrence are known: MEN-1, MEN-2, von Hippel–Lindau syndrome, neurofibromatosis type 1, tuberous sclerosis, Carney's complex, hyperparathyroidism and jaw tumor syndrome, and hereditary paraganglioma–pheochromocytoma syndrome.¹

We report the case of a female patient with several endocrine gland tumors who could a priori be considered as a special case of endocrine tumor syndrome.

This was a 65-year-old woman referred to the endocrinology department of Jaén Hospital due to suspected primary hyperparathyroidism and postmenopausal hirsutism. Her family history included type 2 diabetes in the mother and two hypertensive brothers. Her personal history included HBP, vitiligo, renal colics, and menopause at 51 years of age. She reported increased facial hair and hypertrichosis in the limbs, frontoparietal hair loss and increased libido for the previous three years. There was no evidence of thyroid dysfunction or changes in the neck.

Physical examination findings included: weight 78 kg, BMI 32 kg/m², blood pressure 120/70 mmHg, androgenetic alopecia, and grade 3 hirsutism on the Ferriman–Gallwey scale² with very marked hypertrichosis in the limbs.

Laboratory tests revealed hypercalcemia with elevated PTH, as well as testosterone above the normal range, with no other pathological data (Table 1). Scintigraphy with Tc-99m sestamibi showed a pathological deposit in the right superior parathyroid gland. Thyroid ultrasonography showed

a 2.4 cm × 2 cm × 1.5 cm nodule in the isthmus with benign characteristics. Finally, transvaginal ultrasonography and a CT scan of the abdomen and pelvis were performed with no pathological findings.

Primary hyperparathyroidism was diagnosed, and parathyroidectomy was indicated. During surgery, a thyroid nodule suspicious for malignancy was detected. Intraoperative biopsy suggested a papillary thyroid carcinoma, and total thyroidectomy was therefore performed. After surgery, the patient received ablation therapy with 131I.

Clinical signs of hyperandrogenism persisted, and even worsened, at subsequent visits. An ovarian origin was suspected and, since imaging tests had been negative, the patient was referred to gynecology for exploratory laparoscopy. Bilateral oophorectomy was performed, and a histological diagnosis was made of steroid cell tumor in the right ovary and hyperthecosis and follicular cysts in the left ovary (Fig. 1).

After oophorectomy, a clear improvement was seen in hyperandrogenism, together with partial hair recovery and decreased hirsutism. Hormone tests performed three months later showed a normalization of the biochemical and hormonal parameters (Table 1).

Two years after oophorectomy, the patient was again referred to endocrinology for clinical signs of diabetes and gradual weight loss (10 kg in four months), with a blood glucose level of 342 mg/dL associated with glycosuria and ketonuria. Insulin therapy was therefore started at her health care center. Tests performed showed an HbA1c level of 12.1%, negative GAD and IA2 antibodies, and a C-peptide level of 1.4 ng/dL.

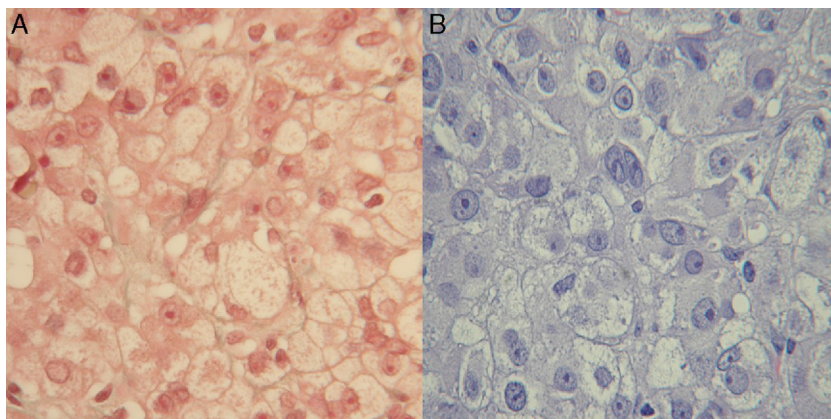
Metabolic control and clinical condition improved after a short period, and the insulin dose was gradually decreased until it was finally discontinued after one year. The patient currently receives oral antidiabetic drugs with an excellent metabolic control (last HbA1c value, 6.2%). Although LADA diabetes was initially considered because of the clinical severity of hyperglycemia, the subsequent course and family history suggested a diagnosis of type 2 diabetes mellitus.

This patient was finally diagnosed with primary hyperparathyroidism (PHP), papillary thyroid carcinoma, ovarian steroid cell tumor, and diabetes mellitus. These conditions may occur sporadically, but the simultaneous occurrence of all of them outside the clinical context of some of the endocrine tumor syndromes reported to date is striking.

☆ Please cite this article as: Moreno Martínez MM, Sánchez Malo C, Gutiérrez Alcántara C, Montes Castillo C, Santiago Fernández P. Diabetes, tumor ovárico, hiperparatiroidismo y cáncer papilar: ¿una asociación casual? Endocrinol Nutr. 2014;61:548–550.

Table 1 Laboratory data before and after surgical procedures (thyroidectomy and oophorectomy).

	Baseline	After parathyroidectomy thyroidectomy	After oophorectomy
Corrected calcium (8.1–10.4 mg/dL)	11.6	10.1	9.8
PTH (7–53 pg/mL)	95.6	57	41
Testosterone (0.3–1.4 ng/dL)	2.54	3.52	0.12
FSH (16–114 IU/L)	15.7	21.9	33.35
LH (10.5–59 IU/L)	7.42	11.7	11.36
SHBG (17–125 nmol/L)	44.9	46	64.3
Free androgen index (0.6–10.6)	19.63	24.43	0.65
DHEAS (μg/mL)	1.06	–	1.1

**Figure 1** Steroid cell tumor: large polygonal cells with vacuolated cytoplasm. (A) Trichromic. (B) H&E.

The association of PHP with medullary thyroid cancer in MEN I and IIA syndromes and with differentiated thyroid cancer outside these syndromes is known. Several cases have been reported in which papillary thyroid carcinoma was found during surgery for PHP. The incidence of PHP combined with thyroid cancer has been estimated at 2–13%.³ Controversy still exists as to whether both conditions are diagnosed at the same time or are caused by common risk factors and/or genetic changes. Mutation in a proto-oncogene responsible for the simultaneous occurrence of papillary and medullary thyroid carcinoma together with PHP has been reported.⁴ It is therefore recommended that, in the presence of PHP, neck ultrasonography should be performed to rule out thyroid nodules requiring investigation for suspected non-medullary thyroid carcinoma.

Our patient had concomitant hyperandrogenism, which based on her obesity and history of PHP could have been related to insulin resistance syndrome, which is present in both conditions.^{5,6} On the other hand, gonadotropin-secreting pituitary tumors have been reported in association with MEN I, which may cause ovarian hyperstimulation.^{7,8} In our case, however, the finding of abnormally low gonadotropin levels for age and the postmenopausal state of the patient suggested ovarian disease.

The resected ovarian tumor, called steroid cell tumor, Grawitz tumor or corticoadrenaloma, shows adrenal cortex remnants on histological examination.⁹ The tumor typically occurs in adult females, especially after menopause. In 70–80% of cases, the tumor has androgenic activity and has virilizing effects. A small proportion of these tumors

may secrete estrogens, and hypercorticism, including the occurrence of diabetes, has been reported,¹⁰ although in our patient this occurred two years after oophorectomy.

The question is to what extent these conditions are mutually independent and are associated by chance, or whether there is some as yet unidentified factor responsible for some predisposition to the development of this type of endocrine disease.

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Dumping syndrome with severe hypoglycemia after Nissen fundoplication in adults. Case report and literature review[☆]



Síndrome de Dumping con hipoglucemia grave tras funduplicatura de Nissen en el adulto. Caso clínico y revisión de la literatura

Gastroesophageal reflux disease (GERD) is the most common esophageal disease. GERD management using antisecretory, prokinetic, and cytoprotective drugs, in addition to hygienic and dietary measures, attempts to relieve the symptoms and to prevent complications (peptic stenosis, Barrett's esophagus, and adenocarcinoma). Surgery is sometimes required, and Nissen—or laparoscopic 360°—fundoplication has been the most widely used antireflux procedure since its introduction in 1991. This surgical procedure achieves satisfactory results in 86–96% of patients, providing functional results similar to the original laparotomy procedure described by Rudolph Nissen (1956). This procedure often has side effects due to anatomic and functional changes, including dysphagia, flatulence, distention, and impossibility to belch and vomit (gas bloat syndrome).

Villet et al. reported accelerated gastric emptying or dumping syndrome (DS) (1978) as a frequent complication of Nissen fundoplication, which occurred in up to 30% of children undergoing this procedure.¹ By contrast, few cases have been reported and well documented in adults.^{2–6}

We report the case of a 21-year-old female patient with a BMI of 27 kg/m² who complained of ascending heartburn for the previous eight years, severe daily acid regurgitation occurring mainly at night with episodes of cough and suffocation, epigastric pain, and mild functional dysphagia which did not improve despite treatment with esomeprazole (80 mg/day).

Work-up was completed with a barium meal test (showing no changes) and upper gastrointestinal endoscopy (which revealed mild peptic esophagitis and incompetence of the cardia). Intraluminal esophageal manometry showed a hypotensive lower esophageal sphincter (8.2 mmHg) with normal esophageal motility, and ambulatory 24-h esophageal pH manometry found a proportion of total time with pH less than 4 of 17.3%, with a DeMeester score of 75.1.

Based on a diagnosis of GERD refractory to medical treatment, the patient underwent laparoscopic surgery consisting of diaphragmatic crura closure and Nissen fundoplication over a 48 Fr. tube. The postoperative course was uneventful, and the patient was discharged on the second day after surgery on a soft diet.

Once at home, the patient started to experience episodes of sweating, dizziness, tremor, and diarrhea two to three hours after meals. Capillary blood glucose levels less than 50 mg/dL were found in several measurements. This delayed her return to work and affected her quality of life.

Abdominal ultrasonography and computed tomography performed due to the occurrence of severe postprandial hypoglycemia showed no pancreatic lesions. An oral glucose tolerance test showed a blood glucose level of 58 mg/dL at 90 min, preceded by a high insulin level (87 nIU/mL). ACTH, cortisol, free T4, and TSH levels were normal. A fasting test was negative, ruling out endogenous hyperinsulinism secondary to insulinoma, nesidioblastosis, or non-tumor induced pancreatogenous hyperinsulinism. A study of gastric emptying by administering a dose of 37 MBq of albumin macroaggregates labeled with Tc99m both as juice and omelette revealed accelerated fluid evacuation. The patient had a good course after the adoption of dietary measures (the avoidance of quickly absorbed sugars and the addition to the diet of complex carbohydrates distributed into five meals). She is currently asymptomatic after three years of follow-up.

DS was described by Hertz in 1913 as an untoward effect of gastroenteroanastomosis, but during the 20th century it was related to gastrectomy, gastrojejunostomy, and vagotomy; it may occur after any stomach surgery (fundoplication, gastrectomy,⁷ or bariatric surgery⁸).

DS is characterized by signs and symptoms divided into two chronological stages. The early/osmotic stage

[☆] Please cite this article as: Roldán Baños S, Ruiz de Angulo Martín D, Munitiz Ruiz V, Martínez de Haro L, Parrilla Paricio P. Síndrome de Dumping con hipoglucemia grave tras funduplicatura de Nissen en el adulto. Caso clínico y revisión de la literatura. *Endocrinol Nutr.* 2014;61:550–551.