CLINCAL CASE

WHEN EVEN THE CLASSICS REQUIRE CLOSE SURVEILLANCE – A TYPICAL CASE OF MEN SYNDROME

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Abstract

The genetic syndrome known in literature as the Multiple Endocrine Neoplasia type 1 (MEN 1) is transmitted in a dominant manner. The primary discovery of more than two endocrine tumor formations representative for MEN 1 should guide the doctor to the suspicion and subsequent confirmation of the diagnosis. Statistics state a long association of the MEN 1 syndrome with the tumors discovered in the small intestine and the pancreas with the adenomas encountered in the parathyroid and pituitary glandular tissueWhile in postmenopausal women, the primary hyperparathyroidism is diagnosed mostly with abnormal levels of parathyroid hormone and serum calcium specifically. The most useful preoperative imaging tools are neck ultrasound scanning and technetium-99m sestamibi scintigraphy. Using bilateral neck exploration, subtotal, and parathyroidectomy are proposed. Our case consists of a 54 years old female, diagnosed with right inferior parathyroid adenoma. With three first degree relatives operated for neuroendocrine pancreatic tumors, her medical history includes distal corporeal-caudal pancreatectomy for a neuroendocrine tumor four years ago. Laboratory tests unveil increased calcium (12, 41 mg/dl) and glucose (150 mg/dl) levels. During hospitalization, the patient's representative parameters for monitoring hyperparathyroidism maintained at high levels. Parathyroid ultrasound and the 99mTc-tetrofosmin/99mTc-pertechnetate parathyroid scintigraphy sustained the diagnosis. Consequently, the patient was proposed for a subtotal parathyroidectomy with a pathology examination. It is highly recommended the interdisciplinary cooperation for the monitoring and management of patients with suspicion of MEN 1. The annual assessment of serum calcium level, together with the parathyroid hormones, is proposed as a screening tool in early diagnosis.

Keywords*: MEN syndrome, parathyroid adenomas, corporeal-caudal pancreatectomy*

Introduction

Multiple endocrine neoplasia type 1 (known as MEN 1) represents a genetic syndrome with an autosomal dominant transmission and affects 2 to 20 per 100,000 people [1]. Tumor suppressor gene MEN 1 encodes the protein menin. The syndrome appears when this gene is inactivated, 90% of the patients have an affected parent, too [2]. In the familial MEN1 form, a first-degree relative of the patient has at least one out of three main glands affected [3]. A cohort of 924 patients

with MEN1 reveals that the older the person, the higher the penetration of the disease. People of all ages can manifest the syndrome. However, the highest prevalence being registered at those under 40 years old [2].

Parathyroid glands, anterior pituitary, and the gastro-entero-pancreatic endocrine cells are the most frequent locations for the MEN tumors [1]. The absence of synchronicity being more of a rule than an exception [4]. A significant concern of the syndrome resides in the malignant potential of pancreatic neuroendocrine tumors (pNETs) [1]. The prevalence of the entero-pancreatic neuroendocrine tumors is 57%, while the one for the parathyroid location is 95% [4].

The most common incriminated cause for hypercalcemia in ambulatory population in Europe and Nord America is primary hyperparathyroidism (PHPT), out of which solitary parathyroid adenomas lead with 80-85% in contrast with hyperplasia affecting more glands found in 15-20% of the cases [5], also associated with a raised incidence of supernumerary or ectopic glands [6]. The last one involving all the four organs implies a family disorder such as MEN1 [5], which is also the most frequently encountered neoplasia in this syndrome (95% of the patients) [6]. PHPT affects mainly women, with a female to male ratio of 3-4:1 [7]. The tumor is often benign, and it has a hyperactive function, thus leading to hyperparathyroidism (HPT) [4].

Postmenopausal women with either elevated or abnormal levels with regard to parathyroid hormone (PTH) and calcium ion, detected in the blood, are diagnosed frequently with primary hyperparathyroidism (PHPT). There were identified three main phenotypes: one with the involvement of the most sensitive systems: renal and skeletal; another with mild asymptomatic hypercalcemia and the last with high PTH levels accompanied by normal serum calcium values [8].

There are differences from the sporadic HPT: mild hypercalcemia, early age of onset of osteoporosis, and a substantial reduction in the mineral density of their bones [6]. The sporadic form appears mostly between 50-75 years old. In contrast, the HPT in MEN 1 syndrome is discovered between 20-30 years old. Also, the serum calcium levels seem not to interfere with the parathyroid hormone secretion [9].

Patients until the age of 50 with asymptomatic PHPT must be referred to a surgeon when during routine blood tests one or more of the following are detected: the serum calcium is equal to, or more than 1 mg/dl, urinary calcium level exceeds 400 mg/24 h, estimated glomerular filtration rate decreases below 60 ml/min/1, 73 m2, in the presence of osteoporosis, nephrolithiasis or nephrocalcinosis [10].

Before surgery, imaging such as ultrasound, 99m Tc-sestamibi nuclear scintigraphy, or CT is offering information on the site of the tumor [7]. However, the most useful preoperative imaging tools are neck ultrasound scanning and technetium-99m sestamibi scintigraphy [11]. Moreover, C-11 methionine PET-CT can be used for a more accurate localization of the hypertrophic parathyroid gland before performing minimally invasive parathyroidectomy [12].

The guidelines have been added to the imaging for kidney stones of nephrocalcinosis, bone density testing of the lumbar spine, hips and non-dominant 1/3 distal radius and the 24-h measurement of urine calcium and creatinine [5]. Despite those, surgeons might also consider omitting imaging tests prior to parathyroidectomy to decrease the overall costs [13].

The bilateral neck exploration (BNE) represents the main surgical approach. Together with parathyroidectomy are associated with a low mortality (0.2%) and morbidity such as wound infection (0.8%), postoperative bleeding (1.5%) recurrent laryngeal nerve (RNL) injury (0.5%) [11].

An open bilateral approach is appropriate in MEN 1 syndrome, where all parathyroid glands are affected. To remove all the abnormal tissue, two surgical procedures are proposed: subtotal parathyroidectomy with the extirpation of 3 glands or total parathyroidectomy. Autotransplantation of a small remnant fragment of the gland placed in the forearm can be included. The main risks are recurrent or persistent disease and permanent hypoparathyroidism. Leaving 40 to 60 g of parathyroid tissue untouched is the main goal in subtotal parathyroidectomy [6]. Minimally invasive parathyroidectomy (MIP) is associated with a cure rate of over 98% in some centers [11].

Surgery contributes positively to an increased quality of life of asymptomatic patients [5]. It is estimated to a percent of 30 people who undergo surgery because of their symptoms or the high serum calcium levels [9]. As for what regards the medical options, cinacalcet is the only one approved until now [5].

Postoperative regular surveillance is advised as the risk of recurrence is estimated to be between 40 and 60% in the first ten years. In the first six months, calcium and PTH levels will be monitored every two weeks and then annually [6]. A MEN 1 carrier shall consider taking an annual immunoassay of a range of hormones, as stated in the guidelines [14].

In the study conducted by Ramos L in 2018 (retrospective cohort study), patients operated for PHPT presented differently than the ones without surgery by higher BMD (bone mineral density) gains, in particular, in two main regions: the lumbar spine and the neck of the femur. Also, the risk of fracture remains the same in both groups [15]. After surgery, BMD improves along with a decrease in the fracture rate, with the only exception of the 1/3 radius and risk of kidney stones [8]. In patients with renal failure, parathyroidectomy associates higher morbidity and mortality because of the interference with the immune and cardiovascular systems [16].

Case presentation

Our case consists of a 54 years old non-smoker and non-alcoholic female, who was presented for medical care because of a right inferior parathyroid adenoma diagnosed one month before presentation in another medical institution.

She has three first degree relatives operated for neuroendocrine pancreatic tumors. Her medical history includes distal corporeal-caudal pancreatectomy with the preservation of spleen for a corporeal-caudal pancreatic neuroendocrine tumor four years ago, followed after two years by uncomplicated diabetes mellitus type II, biliary lithiasis, mixed hyperlipidemia and arthrosis.

Her current treatment includes Controloc 40 mg per day, Creon 10.000 I.U. per day, Crestor, Levemir 15 I.U. per day, and Siofor 1000 mg per day.

The physical examination reveals obesity and abdominal xiphoid-umbilical keloid scar. Laboratory tests unveil increased calcium (12,41 mg/dl) and glucose (150 mg/dl) levels. During hospitalization in the gastroenterology department, a month prior, laboratory tests reveal increased calcium (11,9 mg/dl), glucose (182 mg/dl), and PTH (255,1 pg/ml) levels.

The parathyroid ultrasound revealed: posterior to the inferior half of the right thyroid lobe is outlined a less echogenic to transonic nodule of 8,5/17,6/3,2 mm. Doppler examination highlights intruding vessels. The ultrasound aspect is suggestive for right inferior parathyroid adenoma.

The parathyroid scintigraphy with 99mTc-tetrofosmin or 99mTc-pertechnetate emphasized: at the thyroid gland, right side, the inferior pole, there is evidence of a nodular accumulation with increased FDG uptake on the early parathyroid acquisition with the absence of thyroid scintigraphy, suggestive for parathyroid adenoma. There are no other pathological accumulations in the remaining cervical area or the mediastinum.

Consequently, the patient was proposed for surgery, which consisted of the excision of the right inferior parathyroid gland with the dimensions 1x2 cm and the superior one and thyroid nodule of 0,5x1 cm, respectively. Postoperative we monitored the calcium and the PTH serum levels the patient being discharged with good general condition, without other charges.

Discussions

MEN1 syndrome is known as an autosomal dominant affection (in over 90%) but can occur sporadically, with an incidence of over 0.25% in postmortem studies. The diagnosis of MEN1 syndrome can be made clinically, from family history or genetic tests for a MEN1 specific mutation [16]. The clinical diagnosis is represented by the presence of 2 or more primary endocrine tumors as parathyroid adenomas, enteropancreatic tumors, and pituitary adenomas. The family history diagnosis requires only 1 of the above tumors in a person who has a first-degree relative with a certified diagnosis of MEN1 [16-18].

Adenomas of parathyroid are very frequent in patients with MEN1, in over 90% of cases before 40 years old. The tumors can produce primary hyperparathyroidism, and the patients present with nephrolithiasis, hypercalcemia, and osteitis fibrosa cystica. Our patient presented at 54 years old, but she had medical and familial history. During hospitalization, the patient's calcium level detected in serum and parathyroid hormone were both increased. The age of the beginning of the symptoms of parathyroid adenoma is earlier in cases with MEN1 than in those without, most frequently occurring at 20-25 years compared to patients of 55 years of age [19].

Screening for a parathyroid adenoma using ultrasound is proposed to patients with criteria for hyperparathyroidism. Secondly, because of high sensitivity and specificity (over 90%), the scintigraphy with technetium Tc-99m can be added to the investigation tools to confirm de diagnosis [19-21].

Despite an associated risk, the parathyroid adenomas are often treated effectively using a surgical procedure, either a subtotal or total excision of the parathyroid glands. Because the MEN 1 disease touches more than a gland, the first approach has a relatively increased risk for the maintained a high level of calcium in the blood. In our case, the ultrasound screening helped with the identification of the parathyroid adenoma, later confirmed with scintigraphy [19-20]. The surgery team opted for a subtotal excision of the parathyroid glands, followed by a thorough histopathology examination. The levels of serum calcium and the primary hormone released by the parathyroid glands are recommended to be measured every year for patients with a history of primary hyperparathyroidism and MEN 1 syndrome [21].

Conclusion

The presented case exemplifies a commonly encountered MEN 1 syndrome example. When there is a high clinical, imagistic, or laboratory suspicion for MEN 1, an endocrinology specific assessing must be done, followed closely by suitable laboratory items and targeted imaging. Therefore, the periodical reevaluation of the patient through a multidisciplinary team enhances the long-term prognostic.

Acknowledgment: all authors have contributed equally to this paper.

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