

Clinical Case Seminar

A4(1-5)

An extremely rare association of TSH-secreting pituitary adenoma, metastatic neuroendocrine tumor and Cushing's syndrome in a patient with MEN-1 gene mutation

Giuseppe Giuffrida¹, Erika Messina², Petronilla Daniela Romeo³, Adriana Albani³, Valeria Barresi³, Sergio Baldari⁴, Giuseppe Navarra³, Francesco Ferraù³, Salvatore Cannavò^{2,3}.

¹Department of Clinical and Experimental Medicine, University of Messina; ²Unit of Endocrinology, "G. Martino" University Hospital, Messina; ³Department of Human Pathology of childhood and adulthood "G. Barresi", University of Messina; ⁴Unit of Nuclear Medicine, Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina.

Abstract

Multiple endocrine neoplasia (MEN)-1 syndrome is a rare disorder, due to the loss of function of the tumor suppressor menin. It consists of the association of two or more endocrine tumors, often presenting in a familial setting, being inherited in an autosomal dominant fashion. The most frequent manifestations of MEN-1 syndrome are primary hyperparathyroidism, followed by pituitary adenomas (mainly prolactinomas) and gastrointestinal neuroendocrine tumors, but several other associated conditions have been reported. Herein we describe the case of a male patient, affected by sporadic MEN-1, diagnosed with primary hyperparathyroidism, TSH-secreting pituitary adenoma and bilateral adrenal hyperplasia causing Cushing's syndrome, due to a *de novo* MEN-1 gene mutation. The patient has been successfully treated with first generation somatostatin analog Octreotide LAR (30 mg every 28 days) -with stabilization of the known neuroendocrine lesions and shrinkage of the pituitary adenoma- and with bilateral adrenalectomy. The patient is still regularly followed-up at our Endocrine Unit, and his clinical conditions are stable.

KeyWords: MEN-1, TSH-secreting pituitary adenomas, adrenal hyperplasia, Cushing's syndrome, hyperparathyroidism

Introducing Member: Prof. Salvatore Cannavò

Corresponding Author: Giuseppe Giuffrida - g.giuffrida87@gmail.com

Introduction

MEN-1 syndrome is a rare condition, due to the loss of function of menin oncosuppressor protein (1). It consists of the association of two or more endocrine tumors, and it is generally inherited as an autosomal dominant disorder, although it can rarely occur sporadically (2, 3). The most frequent manifestations of MEN-1 syndrome are primary hyperparathyroidism (PHPT), pituitary adenomas (PA, mainly prolactinomas) and gastrointestinal neuroendocrine tumors (NETs), but several other associated conditions have been reported (2-4). Herein we describe the case of a male patient, affected by PHPT, TSH-secreting PA (TSH-oma) and bilateral adrenal hyperplasia, in the context of a sporadic MEN-1 syndrome.

Case Report

A 61-year-old man was referred to our Endocrine Unit in 2010, since a total-body scintigraphy with ¹¹¹In-Pentretotide (Octreoscan) demonstrated an increased uptake in the right hemithorax, in the mesogastric region, in the liver and in the pituitary gland. He had been followed-up for three years at the Nuclear Medicine Division, after the diagnosis of a primary unknown metastatic NET with multiple repetitive lesions (pulmonary, gastric wall, liver and duodenum). The man had a history of kidney stones, peptic ulcer still treated with protonic pump inhibitors, and arterial hypertension since the age of 40 years. Furthermore, in 2006 he had undergone total thyroidectomy for multinodular goiter, and was prescribed with replacement therapy with levothyroxine, 75 µg per day. Clinical examination was unremarkable, except for a blood pressure of 150/90 mmHg. A thorough biochemical evaluation was performed, including neuroendocrine markers (**Table 1**). Hormonal profile revealed increased free thyroid hormones levels with elevated TSH (23.8 µIU/ml, normal values 0.27-4.2), and slightly increased serum cortisol and urinary free cortisol (UFC) with suppressed ACTH (**Table 1**).

Table 1. Main biochemical data of our patients and their alterations, leading to MEN-1 suspect and diagnosis.

Analyte (unit of measure)	Patient's value*	Normal range
Chromogranin A ng/ml	>1000	<100
Gastrin µIU/ml	811	<100
TSH µIU/ml	23.8	0.27-4.20
FT3 pg/ml	4.13	2-4.4
FT4 pmol/L	38.35	12-22
ACTH pg/ml	<5	0-50
Cortisol µg/dl	27.2	5-25
UFC µg/24h	328	75-270
Calcium mg/dl	10.9	8.2-10.4
PTH pg/ml	228	8-76

Second line biochemical testing confirmed a condition of Cushing's syndrome due to bilateral macronodular adrenal hyperplasia. On the basis of the abnormal uptake within the pituitary gland at Octreoscan and of the inappropriately increased TSH, the patient underwent pituitary MRI, demonstrating a round mass measuring 20 mm in maximum diameter and infiltrating the cavernous sinus, with right deviation of the stalk (**Figure 1**). In the suspect of MEN1, the patient underwent genetic analysis, which revealed a heterozygous c.249_252GTCT MEN1 gene germline mutation; the same analysis resulted negative in his first-degree relatives. Treatment with Octreotide LAR (30 mg s.c. every 28 days) was then initiated, with a significant shrinkage

of the TSH-oma, and normalization of TSH levels after six months of therapy. In addition, the patient underwent bilateral adrenalectomy, obtaining the normalization of glycemic profile and a better blood pressure control under corticosteroid replacement therapy. Finally, in 2015 during follow-up controls, slightly elevated calcium levels and PTH were detected (**Table 1**), suggesting a condition of PHPT, confirmed by a ^{99m}Tc-Mibi scintigraphy showing focal tracer uptake in an area in the right inferior thyroid loggia.

Nevertheless, over the following months, serum and urinary calcium levels were in the normal range, as for normo-calcemic PHPT, with no immediate need for surgery or medical therapy. The patient is still followed-up at our Endocrine Unit, and his clinical conditions remain stable under treatment with Octreotide and the appropriate replacement therapies for adrenal and thyroid function.

The known neuroendocrine lesions are also substantially unmodified at morphological imaging controls.

Discussion.

MEN-1 syndrome is a rare disorder, with an incidence of about 1:30000 (0.25%) in all age groups (from 5 to 81 years). It is transmitted in an autosomal dominant fashion, being mainly a familial disease, although sporadic forms have been reported in about 8-19% of cases (2, 5). MEN-1 syndrome is due to several MEN-1 gene mutations (more frequently deletions) on chromosome 11q13, which codifies for a protein, called menin, involved in several cellular processes and acting as an oncosuppressor (1-3, 6). Patients often present a germinal mutation followed by another mutational event, which determines a loss of heterozygosis (LOH) leading to the development of the disease, according to the so-called Knudson's two-hit hypothesis (1). MEN-1 syndrome is characterized by a high penetrance, since biochemical and clinical manifestations of this disorder usually develop by the fifth decade of age (2). The most frequent (>95% of cases) feature of MEN-1 is PHPT, followed by pancreatic NETs (especially gastrinomas in 40% of cases, and non-functioning NETs in 20-55%) and PA (50%, of which: prolactinomas in 20% of cases; non-functioning and GH-secreting in 10%; ACTH-secreting in less than 5%; TSH-omas in less than 1%; 3, 4). However, in the context of MEN-1 syndrome, other associated features have

Figure 1. MRI revealed a round mass in the left part of the anterior pituitary, measuring about 20x10x10 mm and infiltrating the cavernous sinus, with right dislocation of the stalk.



also been described, including cutaneous manifestations (angiofibromas, lipomas, collagenomas, etc.). Moreover, an involvement of adrenal glands has been reported in 20-70% of cases, ranging from adrenal hyperplasia to adenomas, and rarely carcinomas (2-4), although primary hyperaldosteronism and Cushing's syndrome have been rarely reported (2). MEN-1-related tumors are generally multiple, more aggressive and less responsive to standard treatments when compared with their sporadic counterpart (2, 3). Diagnosis is performed by MEN-1 gene analysis, in patients in whom this condition can be suspected, i.e.: people with two or more endocrine tumors; asymptomatic first-degree relatives of a known MEN1 mutation carrier or a mutation carrier with familial MEN1; individuals with suspicious or atypical MEN1 (parathyroid adenomas before the age of 30; multigland parathyroid disease, gastrinoma, or multiple pancreatic NETs at any age; individuals with two or more MEN1-associated tumors not included in the classic triad of parathyroid, pancreatic islets and pituitary).

In this regard, our case presents several peculiarities. First, the presence of a TSH-oma, a pituitary tumour *per se* very rare, representing less than 1% of PA (7). In a recent case series of 43 patients with TSH-secreting PA, only 2 (4.6%) were affected by MEN-1 (8). On the other hand, the prompt response observed with somatostatin analogs treatment is in agree with previous evidences, confirming the effectiveness of these compounds in controlling hormonal hypersecretion and tumor volume in TSH-omas (9), with a beneficial effect, in our case, also on the coexistent NETs. Second, our patient was diagnosed with bilateral adrenal hyperplasia associated to mild Cushing's syndrome, fully resolved after bilateral adrenalectomy. Another peculiarity is represented by the fact that PHPT, usually an early feature on MEN-1, was only the last manifestation of the disease, thus confirming a great variability in the association patterns of endocrine tumors in this syndrome (6). Furthermore, as a rare finding, our patient had a sporadic form of MEN-1 syndrome deriving from a *de novo* heterozygous germline MEN-1 gene mutation, since none of his first-degree relatives was affected.

In conclusion, attention should be paid in subjects presenting with two or more endocrine tumors, especially when familiar history is suggestive of MEN-1 syndrome. Indeed, an early diagnosis allows to perform an appropriate screening of apparently healthy patient's relatives, and a proper follow-up.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

References

1. Matkar, S., Thiel, A., Hua, X. (2013) Menin: a scaffold protein that controls gene expression and cell signaling. *Trends Biochem Sci*, 38(8):394-402.
2. Thakker, R.V., Newey, P.J., Walls, G.V., Bilezikian, J., Dralle, H., Ebeling, P.R. et al, Endocrine Society. (2012) Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab*, 97(9):2990-3011.
3. Giusti, F., Marini, F., Brandi, M.L. (2005, updated 2017) Multiple Endocrine Neoplasia Type 1. In: Adam, M.P., Ardinger, H.H., Pagon, R.A., Wallace, S.E., Bean, L.J.H., Stephens, K., Amemiya, A., editors, *GeneReviews®* [Internet], Seattle (WA): University of Washington, Seattle; 1993-2018.
4. Carroll, R.W. (2013) Multiple endocrine neoplasia type 1 (MEN1). *Asia-Pacific J Clin Oncol*, 9: 297–309.
5. Giusti, F., Cianferotti, L., Boaretto, F., Cetani, F., Cioppi, F., Colao, A. et al. (2017) Multiple endocrine neoplasia syndrome type 1: institution, management, and data analysis of a nationwide multicenter patient database. *Endocrine*, 58(2):349-359.
6. Marini, F., Giusti, F., Fossi, C., Cioppi, F., Cianferotti, L., Masi, L. et al. (2018) Multiple endocrine neoplasia type 1: analysis of germline MEN1 mutations in the Italian multicenter MEN1 patient database. *Endocrine* (in press), doi: 10.1007/s12020-018-1566-8.
7. Beck-Peccoz, P., Brucker-Davis, F., Persani, L., Smallridge, R.C. & Weintraub, B.D. (1996) Thyrotropin-secreting pituitary tumors. *Endocrine Reviews*, 17:610–638.
8. Valdes Socin, H., Chanson, P., Delemer, B., Tabarin, A., Rohmer, V., Mockel, J. et al. (2003) The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. *Eur J Endocrinol*, 148:433-442.
9. Taylor, T.J, Donlon, S.S., Bale, A.E., Smallridge, R.C., Francis, T.B., Christensen R.S. et al. (2000) Treatment of a Thyrotropinoma with Octreotide-LAR in a Patient with Multiple Endocrine Neoplasia-1. *Thyroid*, 10(11):1001-1007.



©2018 by the Author(s); licensee Accademia Peloritana dei Pericolanti (Messina, Italy). This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>).

Communicated and received February 20, 2018, revised April 20, 2018, published on line June 15, 201