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Case Report

Coexistence of pituitary incidentaloma and primary hyperparathyroidism mimicking multiple endocrine neoplasia Type 1: A case report

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Abstract

The widespread use of imaging procedures has led to an increased discovery of incidental masses in the pituitary gland. Although the majority of pituitary incidentalomas are non-functioning benign adenomas but their increased prevalence poses a diagnostic and therapeutic challenge. These masses may cause various hormonal disturbances as well as they might also be a component of multiple endocrine neoplasia syndromes type 1 (MEN-1) or type 4 (MEN-4). In both syndromes, primary hyperparathyroidism frequently accompanies with pituitary adenomas. Herein we present a 56-year-old man with pituitary incidentaloma who is also detected primary hyperparathyroidism. Contrary to our expectations, any gene defects could be found related with neither MEN-1 nor MEN-4 in the genetic examination.

Keywords: MEN1 Phenocopy; Multiple Endocrine Neoplasia Type 1 (MEN-1); pituitary incidentaloma; primary hyperparathyroidism

INTRODUCTION

The term 'incidentaloma' refers a mass discovered randomly in any organ. These masses may be exist in endocrine organs such as thyroid gland, pituitary gland and adrenal glands as well as in non-endocrine organs including liver, lung and kidneys. With the widespread use of imaging techniques, incidentalomas will be diagnosed more frequently, but also might put burden on the patient due to uncertainty and will have increasing economic consequences for the health system. However, incidentalomas of endocrine glands present additional challenges not only for their high prevalence, but also for the risk of autonomous hormonal activity or for impairing normal glandular function (1). Therefore, a careful and methodical approach should be attempted in evaluation of these masses.

A pituitary incidentaloma is a previously unsuspected pituitary lesion that is discovered on an imaging study performed for an unrelated reason (2). In the largest meta-analysis of autopsy studies, the mean prevalence of pituitary incidentaloma was 10.7% (3). It has been reported that the prevalence of macroadenomas is <1% both in autopsy series (3) and in magnetic resonance imaging (MRI) studies (4, 5). Pituitary tumors are usually benign but can give rise to severe clinical syndromes due to hormonal excess, or to visual/cranial disturbances due to mass effect (6).

The vast majority of pituitary adenomas are sporadic but they might also be related familial pituitary tumor syndromes such as Carney's complex, multiple endocrine neoplasia type 1 (MEN-1) and type 4 (MEN-4). MEN-1 is an autosomal-dominant hereditary syndrome associated with pituitary, parathyroid, and gastroenteropancreatic neuroendocrine tumors (GEP-NET). The syndrome arises from mutations of a gene at chromosome 11q13. This gene encodes a 610-amino acid protein, menin, which is considered a putative tumor suppressor. MEN-4 is a very rare syndrome and has been characterized by parathyroid and pituitary tumors in association with tumors of the adrenals, kidneys, and reproductive organs in both sexes. This syndrome is caused by mutation of Cyclin Dependent Kinase Inhibitor 1B (CDKN1B) gene which is located at chromosome 12p13.1-p12. Firstly, Pellegata et al (7) have identified a germ-line nonsense mutation in the human CDKN1B gene encoding p27, a cyclin-dependent kinase inhibitor that acts as a negative regulator of cell cycle progression.

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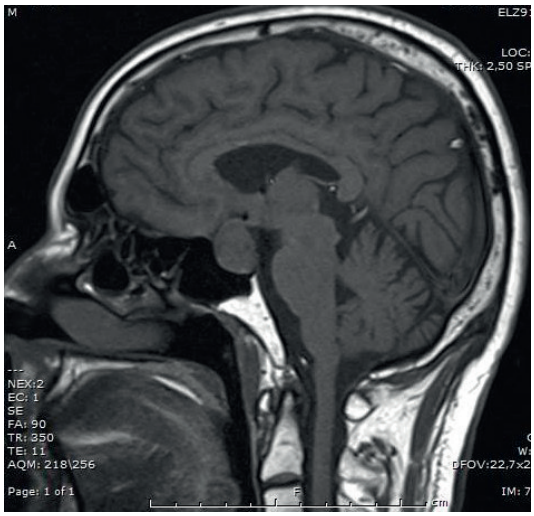
In the light of these informations, we aimed to report this case with coexistence of pituitary macroincidentaloma and parathyroid adenoma who has negative genetic test results in terms of both MEN-1 and MEN-4 and to review the relevant literature.

CASE REPORT

SA 56-year-old male patient had applied to Neurology department of our hospital for headache. A 20 mm sized sellar mass consistent with pituitary macroadenoma was detected on brain MRI (Figure 1), thereupon the patient was referred to our clinic. The patient has no history of chronic illness as well as no family history of pituitary disease, however he complained decreased libido in addition to headache at the last months. On physical examination, there were no remarkable finding except a few brownish skin lesions that are concordant with angiofibromas and collagenomas on abdomen skin (Figure 2). Visual field examination was found normal although pituitary incidentaloma extends to suprasellar region.



The sellar mass extending to suprasellar area on sagittal T1-weighted image

Figure 1. Brain magnetic resonance imaging of the patient

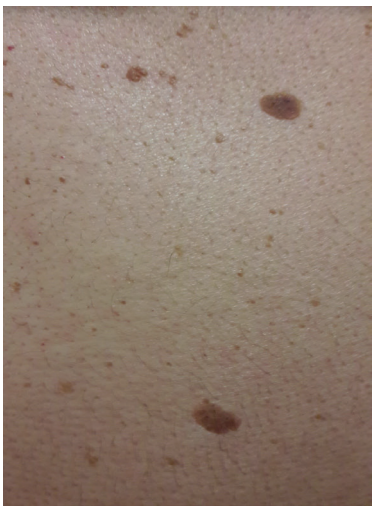


Figure 2. Brownish skin lesions compatible with angiofibroma (a) and collagenoma (b)

Laboratory tests revealed hypogonadotropic hypogonadism and hypercalcemic hyperparathyroidism. On neck ultrasonography, a 2 cm sized hypoechoic nodular area which is consistent with parathyroid adenoma was detected on right inferior loge of the thyroid. Moreover, the presence of parathyroid adenoma was confirmed by Technetium-99m-MIBI scintigraphy (Figure 3). On the other hand, pituitary macroadenoma caused neither hormone hypersecretion nor hypopituitarism except hypogonadotropic hypogonadism. There was coexistence of pituitary adenoma, parathyroid adenoma, and skin collagenoma and angiofibroma that is why we firstly considered the possibility of MEN-1 in our case. We could not detected any evidence for GEP-NET despite the comprehensive examinations both laboratory and radiologically. Chest computed tomography scan and abdominal MRI were normal. The laboratory findings were summarized on Table 1. Based on these results, we reconsidered that our case might be MEN1-like syndrome especially MEN-4. Genetic analysis was also performed for MEN-1 and MEN-4 respectively but both results were found negative.

Table 1. Biochemical and Hormonal Results of the Patient

Test	Result	Reference Range
Glucose	83 mg/dL	70 – 100
Sodium	139 mmol/L	136 – 145
Potassium	4 mmol/L	3.5 – 5.1
Calcium	11.5 mg/dL	8.4 – 10.2
Phosphorus	2.4 mg/dL	2.3 – 4.7
Albumine	4 g/dL	3.5 – 5.2
Parathyroid Hormone	196.9 pg/mL	15 – 68.3
FSH	1.96 IU/L	0.95 – 11.95
LH	0.71 IU/L	0.57 – 12.07
Total testosterone	0.23 µg/L	1.93 – 7.4 *
Prolactin	5.87 ng/mL	3.46 – 19.4
TSH	1.25 µIU/mL	0.34 – 4.94
Free T3	2.38 pg/mL	2 – 4.4
Free T4	0.98 ng/dL	0.7 – 1.48
Cortisol (basal)	9.8 µg/dL	6.2 – 19.4
Cortisol (after 1 mg dexamethasone)	0.8 µg/dL	< 1.8
ACTH	22.5 pg/mL	0 – 46
GH (basal)	0.9 ng/mL	< 5 *
IGF-1	59.9 pg/mL	81 – 225
Insulin	7.77 µIU/mL	2.6 – 24.9
C-peptide	2.48 ng/mL	0.9 – 7.1
Glucagon	78 ng/L	60 – 177
Gastrin	17.9 pg/mL	13 – 115
VIP	< 1.5 pmol/L	0 – 100
Density of Urine	1012 g/mL	1000 – 1030

FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; TSH:Thyroid Stimulating Hormone; T3: Triiodothyronine T4: Thyroxine; ACTH: Adrenocorticotropic Hormone GH: Growth Hormone; IGF-1: Insülin-like Growth Factor-1 VIP: Vasoactive Intestinal Peptide; *according to age

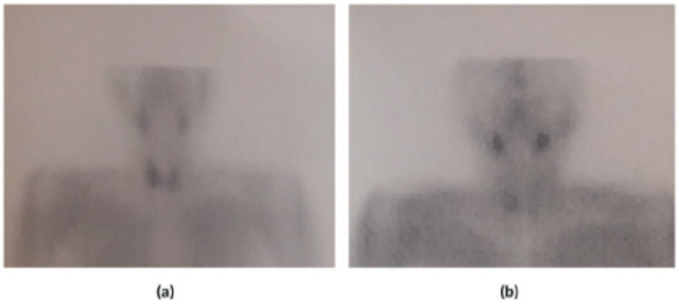


Figure 3. Technetium-99m-MIBI scintigraphy revealed right inferior parathyroid adenoma (a) early image and (b) delayed image

Parathyroid adenoma was excised without any complication. Serum levels of both calcium and parathyroid hormone decreased dramatically after the operation (from 11,5 mg/dL to 9,4 mg/dL and from 196,9 pg/mL to 34,1 pg/mL, respectively). We decided that the pituitary macroadenoma is followed up closely by visual field examination and MRI because of the patient did not have any hormonal disturbance except hypogonadotropic hypogonadism. Testosterone replacement therapy was started to relieve the symptoms of hypogonadism. Neither dimension of pituitary macroadenoma nor visual field examination of the patient changed six months after the first diagnosis. Likewise, any hormonal deficit or hypersecretion did not develop in the course of 1 year clinical follow-up.

DISCUSSION

Pituitary adenomas may lead headache and visual-field defects owing to tumor growth as well as some of these may cause various symptoms due to the syndrome of hormonal excess. The vast majority of these lesions are reported to be non-functioning adenomas. However, non-functioning adenomas may also cause hormonal disturbances such as hypopituitarism or hyperprolactinemia by compression of pituitary gland or pituitary stalk, respectively. It is known that hypogonadotropic hypogonadism is the most common hormonal insufficiency in patients with non-functioning adenoma due to the compression of pituitary gland. Deficits of gonadotropins were revealed in our case, however it was not an unexpected finding because of he has complained libido loss.

Pituitary macroadenomas have more growth tendency as compared with microadenomas. In cases of significant growth of pituitary adenomas during follow-up or the development of compression symptoms such as visual field defects and vision abnormalities, surgical treatment must be strongly considered (2). However, surgery is still controversial in the event of hypopituitarism by itself. Macroadenomas are also the usual cause of hypopituitarism in patients with pituitary incidentalomas (8). Hypopituitarism may improve by surgery in some cases, but it is also possible that worsening of hypopituitarism due to surgery itself. Therefore, it seems reasonable that surgery is considered for younger patients with panhypopituitarism due to compression.

The frequency of multiple endocrine neoplasia syndromes among the people with pituitary incidentaloma is not known exactly. However, it is supposed that these syndromes constitute only a small percentages of pituitary incidentalomas. In patients whose personal or family history suggests the possibility of a multiple endocrine neoplasia syndrome, additional screening and follow-up as appropriate to the suspected syndrome should be undertaken (2). Our case had neither personal nor family history for MEN syndromes, on the other hand both primary hyperparathyroidism (PHP) and skin lesions concordant with angiofibroma and collagenoma were remarkable. As known that PHP is the most frequent and earliest onset manifestation of MEN-1, likewise cutaneous abnormalities such as angiofibromas, collagenomas, lipomas are also common in MEN-1 patients. Therefore, we firstly took into account the possibility of MEN-1. However, any MEN-1 mutation could be detected neither by whole-genome sequencing analysis method nor by multiplex ligation-dependent probe amplification technique using SALSA MLPA probemix kit P017-D1.

The criteria of diagnosis and the indication for MEN1 mutation analysis have been described in the Endocrine Society guideline published in 2012 (9). About 70–80% of typical MEN-1 families harbour MEN-1 mutations, however, in 20–30% of cases that are clinically suggestive of MEN-1, no MEN-1 mutation is found (6). These patients, sometimes termed as having 'MEN-1 phenocopy' can present sporadically or as part of MEN1 families (10, 11). In a recent study, the proportion of phenocopy within the sporadic patients fulfilling the criteria for clinical MEN1 syndrome was found as high as 77% (12). Our case may have been a sporadic MEN-1 phenocopy because he has no family history in terms of MEN-1.

The existence of the tumors in our case may be merely a coincidence because both PHP and pituitary adenomas occur frequently in the general population. However, the exact frequency of combination of these tumors is not known. Based on previous studies, the cooccurence may be estimated approximately 0.8–5.3/10,000 individuals (13,14), therefore, it can be still considered as a rare clinical picture.

On the other hand, screening for CDKN1B gene mutation could be considered in cases that are negative for MEN-1 mutation but display a MEN-1 phenotype. Thus, the possibility of MEN-4 also examined although any tumor of adrenal glands or kidneys did not exist in our case, but no mutation which is related with MEN-4 could be detected in CDKN1B gene by whole-genome sequencing analysis method. Our case had no finding except pituitary adenoma to support Carney's complex that is why we did not need performing genetic analysis for this syndrome.

CONCLUSION

As a consequence, phenocopies which is resemble MEN-1 may cause misdiagnosis in some cases. Therapeutic approaches are similar both MEN1–related and isolated tumors in parathyroid and pituitary glands, however,

regularly follow-up is necessary in terms of development of GEP-NET in the patients with MEN-1. Whereas, no need further examination for GEP-NET in the presence of phenocopy. To distinct of between these two clinical situations may provide to reduce the health-care costs and to alleviate the burdens of anxiety for both the patient and their families. On the other hand, a further <2% of the MEN1 patients without MEN1 mutations may have mutations or gene variants in the cyclin-dependent kinase inhibitor family members, especially CDKN1B (15). Therefore, we also performed genetic examination for MEN-4 but any mutation could not found in CDKN1B gene. Despite the absence of definitive consensus on this issue, genetic analysis should be considered for not only MEN-1 but also MEN-4 in the suspicious cases if the technical facilities are suitable.

Conflict of interest: The authors declare that they have no competing interest.

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