

Atypical clinical manifestations of multiple endocrine neoplasia type 1 syndrome

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KEY WORDS

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ABSTRACT

Multiple endocrine neoplasia type 1 (MEN1) is a hereditary tumor syndrome characterized by a genetic predisposition to develop a variety of neuroendocrine tumors and hormone excess syndromes. The major components of MEN1 are hyperparathyroidism due to multiple parathyroid adenomas or hyperplasia, duodenopancreatic neuroendocrine tumors and pituitary adenomas, most often producing prolactin. Physicians' inadequate knowledge of this clinical entity and sometimes its atypical presentation result in a probable significant underdiagnosis of MEN1. This describes the case of a 65-year-old female in whom primary hyperparathyroidism, limited to only one parathyroid gland, was preceded by acromegaly that was diagnosed 23 years earlier. This case shows that MEN1 manifests itself even in older groups and hyperparathyroidism may not be the first symptom of this syndrome. Therefore, we believe that all subjects who, regardless of age, gender and initial manifestation present with whichever the major symptom should be followed up regularly for the early detection of MEN1.

INTRODUCTION Multiple endocrine neoplasia type 1 (MEN1) is characterized by the coexistence of benign (and very rarely malignant) parathyroid adenomas and hyperplasia, anterior pituitary tumors, neuroendocrine tumors of the digestive system (mainly duodenopancreatic tumors), sometimes accompanied by adrenal and/or thyroid adenomas and dermal and hypodermal tumors.^{1,2} The prevalence of this autosomal dominant inherited clinical entity in the population shows significant differences, reaching from 2 to 20 cases per 100,000 people.³ Lesions observed in patients may develop multifocally within the same gland, bilaterally in multiple glands, and tend to relapse following subtotal removal.⁴ The clinical manifestation of MEN1 is complex and results from hormonal hyperactivity of the hyperplastic glands, mass effect caused by the presence of hypertrophic or tumor lesions (especially of the pituitary gland), and the presence of metastases in the case of malignant tumors.¹ It is assumed that to diagnose MEN1 there is a need to show hyperplasia in at least 2 of the 3 main glands (parathyroid, pituitary, pancreas or duodenum).⁵

Although in many patients making the correct diagnosis is not difficult, there are cases similar to the one described in this paper, when MEN1 has atypical manifestations and its diagnosis may pose a serious diagnostic challenge.

A 65-year-old patient diagnosed with clinically overt acromegaly 24 years earlier was treated in our Department for 3 years. In 1984 she was diagnosed with growth hormone-secreting (GH) hypophysial adenoma of 16 × 14 mm. Bromocriptine treatment was administered (the ward in which acromegaly was diagnosed had little experience in neurosurgery of hypophysial adenomas at that time). Despite increased bromocriptine dosage, the tumor progressed and therefore in 1989 the patient was offered surgical treatment for the headaches and visual disturbances she reported (the symptoms resulted from suprasellar penetration of the tumor). However, the patient refused to undergo surgery and radiotherapy was administered as an alternative treatment. Radiotherapy administered to the sella area resulted in a decrease in the size of the pituitary gland, and after a longer time period, caused the empty sella syndrome. As a result,

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the secretory function of the gland was impaired in thyrotropin secretion (TSH 0.005 mIU/ml), gonadotropin secretion (follicle-stimulating hormone 0.912 U/l, luteinizing hormone – 0.206 U/l) and prolactin secretion (0.308 ng/ml), with the hypothalamic-pituitary-adrenal axis activity values remained close to the lower limit of normal range (adrenocorticotrophic hormone level, 13.0 pg/ml, cortisolemia at 6 a.m., 5.18 µg/dl, at 11 p.m. – 2.6 µg/dl, 24-hour urinary free cortisol, 158.2 µg/24h). In 2002 the patient had bilateral hip joint replacement and because since that time magnetic resonance imaging could not be performed for diagnostic reasons, computed tomography was used. In 2005 high blood levels of insulin-like growth factor (IGF-1) (532 ng/ml, normal value 75–212) and a lack of inhibition of GH secretion (5.49 ng/ml) in the glucose tolerance test accompanied by the empty sella syndrome were observed, which led to the decision that treatment with somatostatin analogs would be necessary. Administration of the maximum dose of long-acting octreotide (30 mg/28 days) lowered IGF-1 levels (to 264 ng/ml) that however did not return to normal. In 2005 symptoms of nodular remodeling of the thyroid were observed for the first time. In a cytological examination features of nodular goiter were observed. The latter has progressed somewhat since diagnosis. In 2007 the patient suffered from weakness and fatigability of proximal muscles of lower limbs, bone pains, and constipation. Osteoporosis diagnosed in the femoral neck and very small subperiosteal erosions of the middle phalanges justified the diagnostic evaluation of calcium-phosphate homeostasis disorders. It showed the increased parathormone level (108.9 pg/ml, normal range, 15–65) and increased serum calcium level (1.456 mmol/l, normal range, 0.98–1.3) with normal 24-hour urinary calcium and phosphate levels. These results suggestive of primary hyperparathyroidism led to the decision to perform parathyroid subtraction scintigraphy that revealed a focal area of increased uptake of ^{99m}Tc MIBI in the upper right parathyroid gland. The diagnosis of primary hyperparathyroidism accompanied by acromegaly led to the suspicion of MEN1 in the patient. Because the patient refused to undergo surgical treatment for hyperparathyroidism, alendronate therapy was administered. Currently, after 12 months of such treatment, the patient remains in a good condition. She is free of clinical symptoms caused by hyperparathyroidism. Abdominal ultrasound and panendoscopy did not reveal the presence of renal, gastric, intestinal, or pancreatic complications of the disease. The patient was administered long-acting octreotide (30 mg/28 days), low dose bromocriptine (2.5 mg daily), alendronate sodium (70 mg/week) and levothyroxine (25 µg daily) for secondary hypothyroidism. For diabetes secondary to acromegaly and somatostatin analog treatment, the patient took also low-dose acarbose (150 mg daily). Serum levels of calcium

(2.48 mmol/l) and phosphate (0.94 mmol/l), together with urinary calcium (3.56 mmol daily) and phosphate levels (18.25 mmol daily) remain within normal ranges. An increase in the parathormone level (98.06 pg/ml) is less significant than at the time of diagnosis of hyperparathyroidism. The free thyroxine level (1.06 ng/ml) and triiodothyronine (3.21 ng/ml) were normal.

DISCUSSION The statistical data concerning the prevalence of MEN1 shown in the introduction suggest that although this endocrine disorder is infrequent, it occurs often enough to be considered in differential diagnosis of any patient with diagnosed hormonal features of hyperparathyroidism, neuroendocrine tumors of the gastrointestinal tract and the pituitary gland. Clinical manifestations of the disease may be discovered in different age groups, and while lesions in one of the glands are observed, there can be detected no abnormalities in other glands. However, in some cases, the course of MEN1 may differ significantly from its typical forms.

Of note, in the patient described here full blown MEN1 developed late, while in most cases (>95%), the syndrome manifests itself by the 5th decade of life.¹ The first manifestation of MEN1 in the patient was acromegaly, which preceded the diagnosis of primary hyperparathyroidism by 23 years. This manifestation was significantly different from the classic forms of MEN1, in which hyperparathyroidism is usually the earliest clinical presentation.² In 98% of all MEN1 cases in which hyperparathyroidism is diagnosed, it was clinically overt by the age of 40, that is, on average, 30 years earlier than in its isolated form.^{3,6} In the described patient, the first manifestation of hyperparathyroidism occurred not earlier than at the age of 64.

Another difference in the observed case was the nature of the lesions of the parathyroid glands. The patient was diagnosed with the enlargement of only one gland, suggesting the presence of an adenoma, whereas in the typical MEN1, hyperplasia occurs in all parathyroid glands.⁷ However, the extent of hyperplasia may be insignificant, and therefore only in 60% of cases – that is much less often than in the sporadic forms – scintigraphy allows to confirm the presence of these lesions (in the remaining cases, diagnosis is made perioperatively).⁵ It must be remembered, however, that the only certain criterion for differentiation between an adenoma and hyperplasia remains the result of histopathological examination, which was impossible to perform because the patient refused to undergo operative treatment. Scintigraphy allows the detection of any parathyroidal tissue able to accumulate a given marker regardless of the cause of the hyperplasia. Asymmetric parathyroid hyperplasia, especially as in MEN1 cannot be excluded. The extent of hyperplasia in the individual parathyroid glands may show marked differences.⁵ The course of hyperparathyroidism was oligosymptomatic because

the only lesions observed were those in bone tissue (osteoporosis, subperiosteal resorption), muscles (weakness and fatigability), functional gastrointestinal disorders (constipation), and symptomatic hypercalcemia, without documented pathology in the kidneys, duodenum and pancreas. It confirmed earlier observations of a rather less aggressive nature of primary hyperparathyroidism, which is part of the MEN1 syndrome.⁷

The treatment of choice for hyperparathyroidism is surgical treatment with either subtotal parathyroidectomy leaving about 20–50 mg of the vascularized tissue in the gland which macroscopically resembles the healthy parathyroid gland, or total parathyroidectomy with autotransplantation of the parathyroid glands.⁵ The described patient did not give her consent to surgery and therefore she had to undergo conservative therapy based on bisphosphonates.⁷ New, the initial results of the treatment are beneficial (subjective and biochemical improvement), but a brief alendronate sodium therapy makes it difficult to assess it unequivocally.

It is estimated that in patients with MEN1, the GH-secreting adenoma constitutes about ¼ of all cases of pituitary tumors.^{1,4} Given the fact that these tumors are observed in 20–30% of MEN1 cases^{1,4}, the prevalence of acromegaly in this syndrome is estimated at 5–7.5%. In the course of MEN1, the GH-secreting adenoma seems to show much more aggressive growth than in the sporadic forms.⁸ This has been confirmed in the current case. After 16 years since radiotherapy, the GH hypersecretion markers have persisted (a lack of inhibition of GH secretion in the glucose tolerance test, increased levels of IGF-1), even though radiotherapy caused the development of the empty sella syndrome and the occurrence of secondary hypofunction of the gonads, thyroid gland, and adrenal glands. Use of long-acting octreotide caused improvement, but not complete normalization of biochemical tests. The course of acromegaly in the current patient must be interpreted with caution because the previous treatment of acromegaly was not optimal from the current point of view. The patient did not agree to undergo surgical treatment which is presently, according to modern standards, considered the treatment of choice; somatostatin analogs were unavailable in therapy at that time; bromocriptine used by the patient at the start of treatment is currently considered to be relatively little effective; and radiotherapy is restricted practically to those refractory to other treatment.⁹

In about 25% of MEN1 cases, focal lesions within the thyroid gland are observed.¹ Although enlargement and nodular lesions of the thyroid were observed in the patient, it is unclear whether their presence showed the cause-effect relationship with MEN1 syndrome. Such association might indicate the very low (because of the secondary hypothyroidism) TSH level, TSH being the key hormone for the thyroid growth process and a crucial

factor in the development of its nodular lesions.¹⁰ On the other hand, it might have been caused by active acromegaly and might have resulted from the action of other growth factors, e.g. IGF-1, on the thyroid tissue. Moreover, the nodular goiter could develop before the development of hypopituitarism and was diagnosed for the first time only in 2005 (diagnostic imaging of the thyroid was not performed earlier).

Although many years have elapsed since the development of acromegaly, no neuroendocrine tumors were observed within the pancreas and other segments of the gastrointestinal tract, whereas their prevalence is estimated at about 60% of cases. Therefore, the lack of lesions in this system does not exclude the presence of MEN1 syndrome. Because lesions with such histologic structure may develop later in life, the patient is being regularly followed for the occurrence of neuroendocrine tumor in the future.

Detection of neuroendocrine tumors and hormone excess syndromes in the patient's family members plays an important role in diagnosing MEN1, however the anamnesis had little value in the current patient (parents died early in a car accident; no siblings or children). It cannot be excluded that clinical signs and symptoms result from a coincidence of hyperparathyroidism and a hypophysial adenoma. Such causal association might be suggested by the late timing of the hyperparathyroidism manifestation and the typical timing of the acromegaly manifestation. It is estimated that in the general population, acromegaly occurs in 60 cases per million people.⁸ On the other hand, diagnosed on the basis of routine serum calcium and serum parathormone measurements in surveys, primary hyperparathyroidism affects 1 per 500 women, with the asymptomatic course in most cases.⁷ An accidental coexistence of GH-secreting hypophysial adenoma and primary hyperparathyroidism is thus extremely rare, with estimated 12 cases per 100 millions women.

In the future evaluation of the described patient, genetic methods could be really valuable, because the cause of MEN1 syndrome is the presence of a mutation of the *MEN1* gene localized on a long arm of the chromosome 11. The gene encodes the 610-amino acid protein – menin – and its physiological function has not yet been fully explored. However menin might play a role of an endogenous tumor suppressor.¹¹ So far, over 200 different mutations, both germinal and somatic, have been identified. They occur with an almost equal frequency within nine out of ten exons of the gene.^{3,11} Even though some mutations have been observed more frequently than others, no hot spots have been identified, which extremely limits the capability of molecular diagnostics¹² and makes it difficult in Poland.

To conclude, the case of the described patient suggests that the course of MEN1 may be variable in patients in terms of its timing, the sequence of manifestations of different symptoms,

observed morphological lesions and the clinical course. Therefore, given the chance of occurrence of MEN1, all patients with hyperparathyroidism, hypophysial adenomas or neuroendocrine tumors of the digestive system should be followed up over many years.

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