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SHORT COMMUNICATION

A novel *MEN1* pathogenic variant in an Italian patient with multiple endocrine neoplasia type 1

Andrea Corsello[1] · Carmine Bruno[1] · Roberta Rizza[2] · Paola Concolino[2] · Giampaolo Papi[1] · Alfredo Pontecorvi[1] · Guido Rindi[3,4] · Rosa Maria Paragliola[1]

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Abstract

The multiple endocrine neoplasia type 1 (MEN1) is a rare syndrome characterized by the predisposition to developing multiple endocrine and non-endocrine tumors, typically characterized by the association between parathyroid gland hyperplasia or tumors, gastroenteropancreatic tumors and pituitary adenomas. The *MEN1* gene is located on the long arm of chromosome 11 (11q13) and it encodes for the protein "menin". We here reported the case of a MEN1-patient, affected by primary hyperparathyroidism, insulinoma, pituitary non-hyperfunctioning adenoma and bilateral adrenal masses, carrying a novel heterozygous pathogenic variant (c.1252_1254delGACinsAT), located in exon 9 of *MEN1* gene.

Keywords MEN1 · Menin · Primary hyperparathyroidism · Insulinoma

Introduction

The multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant tumor syndrome characterized by the predisposition to developing multiple endocrine and non-endocrine tumors [1]. This condition is typically characterized by the association between parathyroid gland hyperplasia or tumors (more frequently adenomas), gastroenteropancreatic tumors and pituitary adenomas occurring in up to 95%, 70% and 40% of cases, respectively [2]. Other endocrine and non-endocrine tumors found with increased frequency are thymic or bronchial carcinoids, adrenocortical tumors, meningiomas, ependymomas, schwannomas, angiofibromas and leiomyomas [3]. The clinical phenotype is therefore heterogeneous both for the variable penetrance of the disease and for the possible influences due to gene-environment interactions.

The gene causing MEN1, the *MEN1* gene, is located on the long arm of chromosome 11 (11q13) and it encodes for the protein "menin", a scaffold protein with tumor suppressor functions. Pathogenic variants of *MEN1* usually have a truncating effect on menin, with loss of the tumor-suppressing function and an increased risk of developing cancer [4]. The prevalence of the syndrome is estimated around 2–3 per 100,000 individuals in Caucasians [3]. Similar data were also reported in nationwide multicenter patients' databases in Asia [5]. Likewise, Italian registry of MEN1 revealed that clinical features are comparable to those of other western countries [6].

The authors Andrea Corsello and Carmine Bruno have equally contributed to this paper.

✉ Rosa Maria Paragliola
rosamariaparagliola@gmail.com

[1] Endocrinology, Università Cattolica del Sacro Cuore, Fondazione Policlinico "Gemelli" IRCCS, Largo Gemelli 8, 00168 Rome, Italy

[2] Institute of Biochemistry and Clinical Biochemistry, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma Largo Gemelli 8, 00168 Rome, Italy

[3] Section of Anatomic Pathology, Dipartimento di Scienze della Vita e di Sanità Pubblica, Università Cattolica del Sacro Cuore, Rome, Italy

[4] Section of Anatomic Pathology, Dipartimento di Scienze della Salute della Donna, del Bambino e di Sanità Pubblica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma Largo A. Gemelli 8, 00168 Rome, Italy

Case report

We here describe the case of a MEN1-patient carrying a novel *MEN1* mutation. A 40-year-old patient, with a previous diagnosis of 4 mm pituitary adenoma incidentally discovered at magnetic resonance imaging performed for headache, presented to our hospital for asymptomatic hypercalcemia and hypoglycemia with mild neuroglycopenic symptoms. Biochemical evaluation confirmed primary hyperparathyroidism (serum calcium 11.1 mg/dl; phosphorus 2.2 mg/dl; PTH 287 pg/ml) due to right inferior hyperplastic parathyroid, detected at ultrasonography and Tc-99m MIBI scintiscan. Accordingly with primary hyperparathyroidism, the patient presented with osteoporosis and kidney stones detected at abdominal CT scan. During hospitalization, hypoglycemia with inappropriately high-normal insulin levels was detected (glycemia: 48 mg/dl; insulin 7 mcU/ml; C-peptide 0.9 ng/ml). Abdominal CT scan showed two lesions suspicious for multifocal insulinoma, located in the pancreas tail, of about 6 and 1 cm. Endoscopic ultrasonography with fine-needle aspiration biopsy was performed and the histology was suggestive for well-differentiated neuroendocrine tumor G2, showing positivity for insulin. At abdominal CT scan, bilateral adrenal masses (29 mm and 32 mm in the left adrenal gland and 17 mm and 9 mm in the right adrenal gland) were incidentally discovered. The biochemical assessment of adrenal and pituitary function confirmed that neither the adrenal masses nor the pituitary adenoma were hyperfunctioning. Furthermore, an angio-CT scan was performed for the suspicion of thoracic aortic aneurysm. No lesion suggestive for bronchial or thymic carcinoid was detected. In December 2019, the patient underwent subtotal parathyroidectomy and final histology confirmed parathyroid hyperplasia (Fig. 1a). The patient developed hypoparathyroidism and he is now on replacement therapy with calcitriol 1 mcg/day and calcium per os (2 gr/day). In April 2020, the patient underwent en-bloc subtotal splenopancreasectomy, left adrenalectomy and lymphadenectomy. Formalin fixed paraffin embedded sections were stained with hematoxylin and eosin (H&E) for histopathology assessment. Immunohistochemistry for insulin was performed with Dako Omnis Agilent standard routine protocols with a guinea pig polyclonal antibody to human insulin (code A0564, Dako, Milan, Italy). Final histology

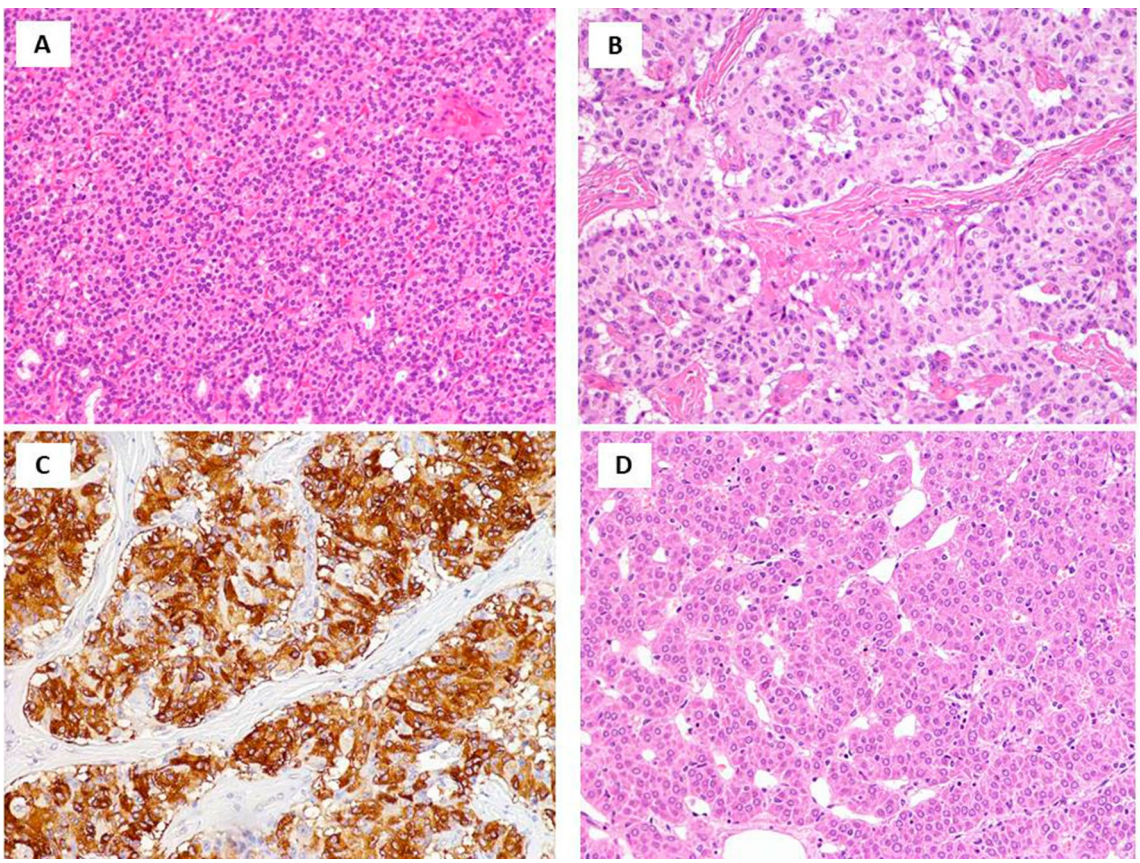

Fig. 1 Final histology of parathyroid hyperplasia (**a***), well-differentiated insulinoma (**b*** and **c**°) and adrenal oncocytic adenoma (**d***). *Hematoxylin and eosin original magnification × 200; °immunoperoxidase, original magnification × 200

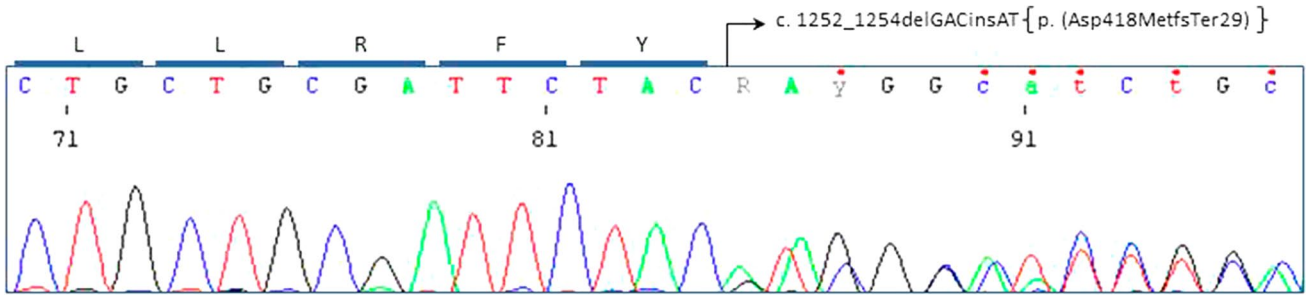

Fig. 2 Electopherogram shows the c.1252_1254delGACinsAT pathogenic variant in exon 9 of the MEN1 gene. This frameshift mutation involves the deletion of three nucleotides (GAC) and the insertion of other two bases (AT) causing a premature stop codon at aminoacid 447

confirmed multiple (five lesions between 2.6 and 0.3 cm) well differentiated G1 and G2 neuroendocrine tumors, the largest one positive for insulin (Fig. 1b and c). Metastases was observed in two peripancreatic lymph-nodes [pT3m, N1 (AJJC 2017)]. Adrenal gland final histology showed adrenal oncocytic adenoma (Fig. 1d).

In line with current clinical practice guidelines, genetic counseling and molecular analysis of the *MEN1* gene was performed after a written informed consent was obtained. Genomic DNA was extracted from peripheral lymphocytes and the whole coding sequence and exon-intron junctions of the *MEN1* gene were amplified and sequenced. Five couples of primers (sequences available on request) were used to amplify the ten exons of the gene. The PCR products were directly sequenced using BigDye Terminator Cycle Sequencing kit v3.1 (Applied Biosystems, USA) and ABI 3100 Avant Genetic Analyser (Applied Biosystems, USA) according to manufacturer's instructions. Sequencing electropherograms were analyzed against the references sequence NG_008929.1 and NM_130799.2 using the SeqScape v3.0 software package (Applied Biosystems, USA).

Sequencing analysis revealed a novel heterozygous pathogenic variant, the c.1252_1254delGACinsAT; p.(Asp418MetfsTer29), located in exon 9 of the gene (Fig. 2). This frameshift mutation, causing a stop codon at aminoacid 447, is predicted to lead to a truncated protein. In a previous paper, considering all *MEN1* germline mutations reported from 1997 to 2015 worldwide, *MEN1* codons most affected by mutations have been evaluated [4]. Most of these codons were located in exons 2, 9 and 10 where specific hot spots may be associated with DNA sequence repeats, consisting of long tracts of either single nucleotides or shorter elements ranging from dinucleotides to octanucleotides [4]. The novel c.1252_1254delGACinsAT variant is added to the other seven mutations [7–12] involving the codon 418 in exon 9 (Fig. 2). So far a total of eight pathogenic variants, affecting the 418 codon (nucleotides:1252–1254), have been reported. Three of these variants (c.1252G > A, c.1252G > C, c.1252G > T) involve the substitution of a single nucleotide producing the change of the wild-type p.Asp418 amino acid with a different residue. The remaining five variants are all frameshift mutations (c.1252_1263del12bp; c.1253_1254delAC; c.1253_1255delACG; c.1254delC; c.1252_1254delGACinsAT) causing the deletion of one or more nucleotides and the premature truncation of the protein. Based on these data, the 418 codon is one of the most affected codons of MEN1 protein, resulting in a specific mutational hotspot. A genetic test has been offered to the patient's relatives (two sons), but given the current SARS-CoV-2 pandemic in Italy and the consequent lockdown, all non-essential clinical procedures have been postponed.

Conclusion

We report a novel heterozygous pathogenic variant, located in exon 9 of *MEN1* gene detected in a patient affected by MEN1, presenting with primary hyperparathyroidism, insulinoma, pituitary non-hyperfunctioning adenoma and bilateral adrenal masses. Even if the detection of a specific *MEN1* mutation may be of limited significance for the clinical management and most studies have shown that *MEN1* mutations usually do not show a clear genotype-phenotype correlation, it is not possible to exclude that this newly reported mutation is not associated with a specific clinical presentation. Moreover, the patient is a 40-year old man and he has already presented with all the classical manifestation of MEN1, including the rarer conditions of insulinoma and bilateral adrenal masses. Therefore, it is necessary to establish a regular follow-up to monitor for possible peculiar clinical evolution. Furthermore, the novel mutation described has been identified in the 418 codon that represents a specific mutation hotspot and is useful to screen the first-degree relatives to identify possible pre-symptomatic carriers. The wide variability in clinical presentation of MEN1 syndrome, makes useful to report novel mutations, to better understand the possible clinical evolution of the syndrome.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli IRCCS of Rome.

Informed consent A written informed consent was obtained from the patient for the publication of this case report.

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