Scientific Research Publishing

Open Journal of Endocrine and Metabolic Diseases, 2026, 16(5), 121-128
https://www.scirp.org/journal/ojemd
ISSN Online: 2165-7432
ISSN Print: 2165-7424

Association between MEN1 and Medullary Thyroid Carcinoma: Myth or Reality?

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How to cite this paper: Srifi, H., Riznat, M., Mohamed, M., Issouani, J. and Guerboub, A.A. (2026) Association between MEN1 and Medullary Thyroid Carcinoma: Myth or Reality? *Open Journal of Endocrine and Metabolic Diseases*, **16**, 121-128.
https://doi.org/10.4236/ojemd.2026.165013

Received: April 5, 2026
Accepted: May 8, 2026
Published: May 11, 2026

Abstract

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant genetic disorder characterized by the association of parathyroid, pituitary, and gastro-enteropancreatic neuroendocrine tumors. Medullary thyroid carcinoma, on the other hand, is the major manifestation of MEN2. The coexistence of MEN1 and medullary thyroid carcinoma is exceptional and controversial. This review aims to analyze the available data and clarify the possible existence of a pathophysiological link.

Keywords

Multiple Endocrine Neoplasia Type 1, Thyroid Cancer, Papillary Thyroid Carcinoma, Case Report

1. Introduction

Medullary thyroid carcinoma is a rare neuroendocrine tumor arising from the parafollicular C cells of the thyroid gland, accounting for approximately 1% to 2% of thyroid cancers. It occurs sporadically in the majority of cases or in a familial context, most often as part of Multiple Endocrine Neoplasia type 2, linked to a germline mutation in the RET gene. In this context, medullary carcinoma is the main manifestation of the syndrome and may be associated with other endocrine disorders, including pheochromocytoma and hyperparathyroidism [1].

Conversely, Multiple Endocrine Neoplasia type 1 is a distinct genetic disorder linked to a mutation in the MEN1 gene, which codes for menin. It is classically characterized by the association of primary hyperparathyroidism, pituitary adenomas, and gastroenteropancreatic neuroendocrine tumors [2].

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Medullary carcinoma is not part of the usual tumor spectrum of this condition. Therefore, the association between multiple endocrine neoplasia type 1 and medullary thyroid carcinoma remains exceptional and is rarely reported in the literature.

2. Observation

We report the case of a 43-year-old female patient with no known family history of multiple endocrine neoplasia or hereditary thyroid disease, referred for investigation of a mid-lobe thyroid nodule discovered incidentally during a routine clinical examination.

A chronological summary of the clinical course is as follows: incidental discovery of a thyroid nodule, followed by total thyroidectomy and diagnosis of medullary thyroid carcinoma; one year later, development of hyperprolactinemia revealing a prolactinoma; subsequently, occurrence of chronic diarrhea with marked hypergastrinemia leading to suspicion of gastrinoma; and finally, genetic confirmation of Multiple Endocrine Neoplasia type 1 (MEN1), followed by regular endocrine follow-up.

The clinical examination revealed no palpable cervical lymphadenopathy, no compressive signs, and no manifestations suggestive of an associated endocrinopathy.

A cervical ultrasound revealed a hypoechoic, mid-lobular thyroid nodule with irregular borders and no obvious microcalcifications. In view of these suspicious ultrasound features, and as part of the workup for a thyroid nodule, a serum calcitonin level was measured, which was found to be markedly elevated (>100 pg/mL), strongly suggestive of medullary thyroid carcinoma.

The patient underwent a total thyroidectomy combined with prophylactic central lymph node dissection. The postoperative course was uneventful, with no hypocalcemia or laryngeal complications.

The histopathological examination confirmed the diagnosis of medullary thyroid carcinoma. The tumor was unifocal, confined to the thyroid gland, without capsular invasion or extrathyroidal extension. No lymphovascular invasion was identified. There was no evidence of multifocal tumor involvement. The adjacent thyroid parenchyma showed no C-cell hyperplasia. Examination of the central compartment lymph nodes revealed no metastatic involvement.

Serum calcium and parathyroid hormone (PTH) levels were within normal ranges, and there was no evidence of primary hyperparathyroidism, thus helping to further characterize the MEN1 phenotype in this patient.

As part of the etiological assessment, a genetic analysis searching for germline mutations in the RET proto-oncogene was carried out and proved negative. No somatic tumor analysis was performed; therefore, the medullary thyroid carcinoma was considered apparently sporadic.

One year after surgery, the patient presented with secondary amenorrhea associated with spontaneous bilateral galactorrhea. The patient's history revealed no

medication use that could explain these symptoms. Hormonal testing showed significant hyperprolactinemia. Pituitary magnetic resonance imaging revealed a pituitary microadenoma measuring 8 mm along its longest axis, consistent with a prolactinoma.

Treatment with cabergoline was initiated at a low dose with gradual titration. The outcome was favorable, marked by the disappearance of galactorrhea, the resumption of menstruation, and the normalization of prolactin levels. Follow-up MRI showed progressive regression of the adenoma's size until its complete disappearance, allowing treatment to be discontinued after sustained normalization.

During follow-up, the patient experienced several episodes of chronic watery diarrhea without any associated infectious syndrome. Laboratory tests revealed a significant elevation of gastrin levels, exceeding 20 times the upper limit of normal, confirmed on several samples.

The patient was not receiving proton pump inhibitors at the time of evaluation. Gastric acidity was not directly measured; however, the marked elevation of gastrin levels in this clinical context strongly suggested inappropriate hypergastrinemia. Imaging studies were performed to localize the lesion, supporting the diagnosis of a gastrin-secreting neuroendocrine tumor.

All the clinical and biological data were in favor of a secreting neuroendocrine tumor.

Given the association of a secreting pituitary adenoma and a gastrinoma, the hypothesis of Multiple Endocrine Neoplasia type 1 (MEN1) was considered. Molecular genetic analysis was performed and revealed a germline mutation in the MEN1 gene encoding menin, thus confirming the diagnosis of MEN1.

Thus, this patient presented with an unusual association of apparently sporadic medullary thyroid carcinoma, confirmed by the absence of RET germline mutations and C-cell hyperplasia, with multiple endocrine neoplasia type 1, diagnosed subsequently following the development of a prolactinoma and a gastrinoma. This rare coexistence highlights the importance of comprehensive and long-term endocrine follow-up in such patients.

3. Discussion

Medullary thyroid carcinoma is a neuroendocrine tumor arising from the parafollicular C cells of the thyroid, representing approximately 1% to 2% of all thyroid cancers. It occurs sporadically in nearly 75% of cases and in a familial context in approximately 25% of cases, primarily within the framework of Multiple Endocrine Neoplasia type 2. Familial forms are linked to germline mutations in the RET proto-oncogene and are generally characterized by multifocal, bilateral involvement preceded by C-cell hyperplasia. These histological features constitute major evidence in favor of a syndromic origin [1].

Conversely, Multiple Endocrine Neoplasia type 1 (MEN1) is an autosomal dominant genetic disorder linked to a mutation in the MEN1 gene, which codes for menin. It is characterized by the classic association of primary hyperparathy-

roidism, gastroenteropancreatic neuroendocrine tumors, and pituitary adenomas. Other tumor locations may be observed, including adrenal, thymic, or bronchial tumors. In contrast, the thyroid involvement described in MEN1 is essentially benign nodules or differentiated carcinomas, and medullary carcinoma is not part of the usual tumor spectrum [2].

In our observation, several arguments support a diagnosis of sporadic medullary carcinoma. The tumor was unifocal, without C-cell hyperplasia and without lymph node involvement. Furthermore, genetic testing did not reveal any mutations in the RET gene. These characteristics are classically associated with sporadic forms of medullary carcinoma and contrast with the familial forms observed in MEN2 [3].

The secondary occurrence of a prolactinoma and then a gastrinoma led to the suspicion of MEN1. This suspicion was confirmed by the identification of a germline mutation in the MEN1 gene [4].

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant genetic disorder caused by inactivating mutations in the MEN1 gene. Its incidence is estimated to be between 1 in 10,000 and 1 in 100,000 individuals. The MEN1 gene is a tumor suppressor gene located on chromosome 11q13. It spans approximately 9 kilobases and comprises 10 exons, with exons 2 through 10 being the coding regions. This gene codes for menin, a nuclear protein composed of 610 amino acids, which is ubiquitously expressed in many tissues.

Menin plays a crucial role in regulating cell proliferation, gene transcription, genomic stability, and cell cycle control. It interacts with several transcription factors and chromatin remodeling complexes, thus contributing to the maintenance of cellular homeostasis. Inactivating mutations in the MEN1 gene lead to a loss of menin function, promoting uncontrolled cell proliferation and the development of multiple endocrine tumors.

From a pathophysiological standpoint, MEN1-associated tumorigenesis generally follows the tumor suppressor gene model, involving a two-step mechanism with an initial germline mutation followed by a second somatic event, most often a loss of heterozygosity at the MEN1 locus. This complete gene inactivation leads to total loss of menin function and promotes tumor development in target tissues [5] [6].

Two forms of Multiple Endocrine Neoplasia type 1 (MEN1) have been classically described: a sporadic form and a familial form. The sporadic form is defined by the presence, in the same patient, of at least two of the three main endocrine lesions characteristic of the disease, namely primary hyperparathyroidism, gastroenteropancreatic neuroendocrine tumors, and pituitary adenomas. In this situation, the absence of a family history does not rule out a genetic origin, as de novo germline mutations of the MEN1 gene can be observed. Thus, a significant proportion of patients initially considered sporadic actually have a germline mutation identified during molecular analysis.

Conversely, the familial form is diagnosed when at least one first-degree relative has one of the endocrine tumors characteristic of MEN1, or when a germline mu-

tation of the MEN1 gene is identified in several members of the same family. This form is transmitted in an autosomal dominant manner, with high penetrance and variable clinical expression from one individual to another. Manifestations can appear at different ages and affect various endocrine organs, explaining the phenotypic heterogeneity observed within the same family.

The distinction between sporadic and familial forms is of major clinical importance. It determines whether a family history is necessary, whether genetic screening is implemented in at-risk relatives, and whether early longitudinal follow-up is established. Indeed, the identification of a germline mutation in the MEN1 gene allows for systematic monitoring aimed at the early detection of various associated tumor manifestations, thus improving the management and prognosis of affected patients [7] [8].

The association of medullary thyroid carcinoma and MEN1 is exceptional. To date, only a few isolated cases have been reported in the literature, without a clear pathophysiological relationship being demonstrated [9] [10].

Compared with previously reported cases, our observation shares similarities such as the absence of RET mutation and the occurrence of medullary thyroid carcinoma outside the classical MEN1 spectrum. However, unlike some cases where loss of heterozygosity (LOH) of the MEN1 gene was demonstrated in tumor tissue, this analysis was not performed in our patient, limiting mechanistic interpretation.

In 2014, Lucie Bohacek reported the first case describing the association between Multiple Endocrine Neoplasia type 1 (MEN1) and medullary thyroid carcinoma in a 60-year-old Canadian patient. This patient presented with a familial form of MEN1 involving a prolactinoma, a pancreatic neuroendocrine tumor, and a parathyroid adenoma. Several years after surgery for persistent hyperparathyroidism, a total thyroidectomy was performed due to thyroid nodules. Histopathological analysis revealed medullary thyroid carcinoma. In the absence of genetic testing, particularly of the RET gene, the sporadic or syndromic origin of this carcinoma could not be determined, leaving open the question of a pathophysiological link between these two entities [11].

Two years later, Aranda Velázquez reported a similar case in a 44-year-old Spanish patient with familial multiple endocrine neoplasia type 1 associated with several neuroendocrine tumors. Medullary thyroid carcinoma was discovered incidentally during histological examination of the thyroid tissue. Molecular analysis revealed loss of heterozygosity of the MEN1 gene within the tumor, without mutation of the RET gene, suggesting that complete inactivation of MEN1 may have played a role in medullary tumorigenesis.

To date, only the case described by Aranda *et al.* has been formally identified as a case of CMT secondary to loss of heterozygosity of the MEN1 gene appearing in the context of MEN1 syndrome [12].

Indeed, loss of heterozygosity of the MEN1 gene constitutes a second inactivating event responsible for the complete loss of menin function. This inactivation promotes the proliferation of thyroid C cells, genomic instability, and the acqui-

sition of additional abnormalities, which can exceptionally lead to the development of medullary thyroid carcinoma [12].

Overall, given the extremely small number of reported cases and the heterogeneity of molecular findings, this association is most likely coincidental, although a causal relationship cannot be completely excluded.

In our case, loss of heterozygosity analysis was not performed due to limited technical resources.

It is important to note that, although thyroid involvement is not part of the classic tumor spectrum of Multiple Endocrine Neoplasia type 1, several types of thyroid tumors have been reported in the literature. These include primarily papillary thyroid carcinoma and oncocytic thyroid carcinoma. These observations suggest that the involvement of the MEN1 gene in thyroid tumorigenesis may extend beyond classically described endocrine locations, although the pathophysiological link remains under discussion [13] [14].

There are essentially two possible explanations for this association: a hereditary predisposition to CMT linked to the MEN1 gene, or sporadic CMT developing in a patient with MEN1 syndrome.

Several hypotheses can be discussed. The first, and most likely, is that of a chance association between two independent pathologies.

This hypothesis is supported by the absence of a RET mutation and the absence of C-cell hyperplasia. The second hypothesis would be that of a double independent germline mutation involving both the MEN1 and RET genes. However, this situation was not found in our patient. A third hypothesis suggests a potential role for menin in neuroendocrine tumorigenesis, including thyroid C cells. However, the available experimental data remain limited, and clinical studies have not shown an increased incidence of medullary carcinoma in patients with MEN1, apart from the reported case of ARANDA.

Clinically, this observation underscores the importance of a cautious diagnostic approach to medullary thyroid carcinoma. In the presence of medullary thyroid carcinoma with a negative RET mutation, the sporadic form should be considered. However, the subsequent development of other endocrinopathies should raise suspicion of a distinct multiple endocrine neoplasia. In our case, the appearance of a prolactinoma and a gastrinoma led to the investigation of MEN1, which was genetically confirmed.

This observation also highlights the importance of long-term follow-up for patients with endocrine tumors, even after treatment of the first neoplasm. The sequential discovery of multiple endocrine tumors should lead to a comprehensive diagnostic reassessment and appropriate genetic testing.

Finally, it is important to emphasize that in patients with a MEN1 gene mutation in the context of Multiple Endocrine Neoplasia type 1, tumorigenesis classically relies on a two-step mechanism involving the complete inactivation of the tumor suppressor gene. This inactivation most often occurs through loss of heterozygosity (LOH) at the tumor site, leading to loss of menin function and dysreg-

ulation of cell proliferation control. Although the usual manifestations of MEN1 primarily involve primary hyperparathyroidism, pancreatic neuroendocrine tumors, and pituitary adenomas, rarer locations have been described. In particular, the association with medullary thyroid carcinoma remains exceptional but has been reported in the literature, notably in cases where loss of heterozygosity of the MEN1 locus has been demonstrated in thyroid tumor tissue. This suggests that complete inactivation of the MEN1 gene could, in rare cases, promote the proliferation of thyroid C cells and contribute to medullary tumorigenesis, independently of the abnormalities usually involved, particularly those of the RET gene. In this context, and although current recommendations do not systematically advocate this screening, some authors suggest that biological monitoring by calcitonin measurement could be considered in patients carrying a MEN1 mutation, especially in the presence of suspected complete gene inactivation. This approach aims to enable the early diagnosis of medullary thyroid carcinoma, the early detection of which determines the prognosis.

Finally, although current guidelines do not recommend routine calcitonin screening in MEN1 patients, some authors have suggested—based only on isolated case reports—that calcitonin monitoring could be considered as a hypothesis in selected situations. However, this remains speculative and unsupported by robust evidence.

4. Conclusion

The association between multiple endocrine neoplasia type 1 and medullary thyroid carcinoma remains exceptional. Our observation likely suggests a chance coexistence, although a potential role for complete inactivation of the MEN1 gene cannot be entirely ruled out. Vigilant diagnosis and long-term follow-up of patients with multiple endocrine tumors are necessary.

Consent for Publication

Written informed consent was obtained from the patient for the publication of this clinical case.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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