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Case Report

# Clinical implication of *MEN1* mutation in surgically resected thymic carcinoid patients

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**Abstract:** Thymic carcinoid is a rare but very aggressive neuroendocrine tumour derived from the neuroendocrine system. Here we report a male patient with thymic atypical carcinoid. Though thymic carcinoid is relatively common, the gene sequencing profile was performed and the gene sequencing result indicated germline multiple endocrine neoplasia type 1 (MEN1) mutation and two somatic mutations on *MEN1* gene and no copy number variation or fusion events were detected. It is well-known that the mutation of MEN1 is the typical manifestation of MEN1 syndrome, which is an autosome dominant disease that includes varying combinations of more than 20 endocrine and non-endocrine tumors. In the English literature, 7 cases of solitary thymic carcinoid harboring somatic variants in MEN1 are reported in the absence of other organs involvement as MEN1 syndrome presents. We summarized the clinical features and prognosis of this rare thymic tumor.

**Keywords:** Multiple endocrine neoplasia type 1 (MEN1); thymic carcinoid; next generation sequencing (NGS); prognosis

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## Introduction

Thymic carcinoid refers to a neuroendocrine tumour arising in the thymus, accounting for about 2–7% of anterior mediastinal masses (1,2). Approximately 40% of patients have Cushing syndrome as a result of adrenocorticotropic hormone secretion by the tumour (1). Since the initial report of thymic carcinoid by Rosai and Higa in 1972 (3), about 200 cases of thymic carcinoid have been reported in English literature so far. We describe a 62-year-old male patient with surgically resected thymic carcinoid and mutations of *MEN1* gene were detected by next generation sequencing (NGS). Previous evidence indicates that thymic carcinoids occur in 1–5% of patients with multiple endocrine neoplasia type 1 (MEN1) syndrome and are a major cause of morbidity and mortality (4). We did a literature review and analyzed the clinicopathologic characteristics of all thymic carcinoid patients with the initial manifestation of MEN1 syndrome. All of thymic carcinoids patients with somatic mutation of *MEN1* gene had MEN1 syndrome. Considering none of other organs involved and a negative family history of MEN1 syndrome, our patient could not be diagnosed with MEN1 syndrome at this moment. Based on the findings of our literature review, we proposed that somatic mutation test of *MEN1* gene and evaluation of other organs are recommended for thymic carcinoid patients. Moreover, close follow-up of thymic carcinoid patients with somatic mutation of *MEN1* gene is necessary and could help detect disease recurrence and metastases early.

## Case presentation

A 62-year-old male patient was admitted to the hospital

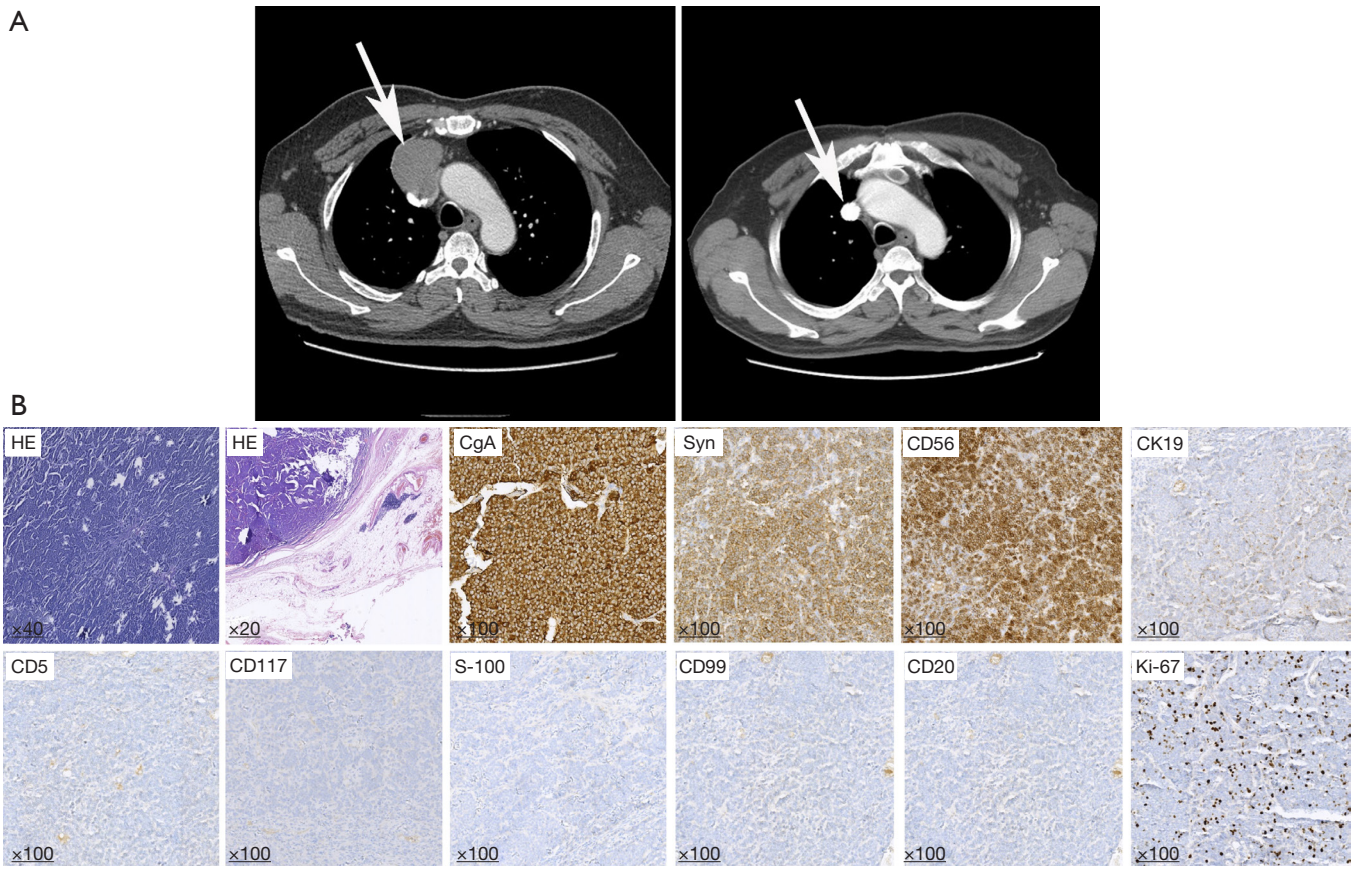


**Figure 1** CT images and pathological stainings. (A) *Left*: preoperative CT image. Arrow indicates that anterior mediastinum invades the superior vena cava. *Right*: postoperative CT image. Arrow indicates artificial blood vessel reconstruction; (B) HE and IHC stainings. CT, computed tomography; HE, hematoxylin and eosin; IHC, immunohistochemistry; CgA, chromogranin A.

because of chest discomfort in June 2015. An enhanced chest computed tomography (CT) showed an anterior mediastinum mass invading superior vena cava, approximately 6 cm × 5 cm × 2 cm in size (*Figure 1A*). Positron emission tomography indicated the mass had an abnormal 18F-fludeoxyglucose (FDG) uptake and a preliminary diagnosis of malignant anterior mediastinum mass was given. Physical examination, laboratory evaluation, and radiological tests of other organs revealed no significant abnormalities. A resection of mediastinum mass together with systemic lymphadenectomy and artificial blood vessel reconstruction was performed using a midline approach through a sternotomy. Macroscopically, the mass was 5.5 cm × 4.5 cm × 2.2 cm with gray, soft and smooth section. Microscopically, postoperative hematoxylin and eosin (HE) staining showed thymic tissue, together with 2–4 nuclear mitosis per 10 HPF and focal necrosis. And immunohistochemistry (IHC) staining was positive for chromogranin A (CgA), Syn, CD56, CK19 and negative for CD5, CD117, S-100, CD99, CD20 with a Ki-67 index of 15% (*Figure 1B*). Through HE and IHC stainings, the diagnosis of thymic atypical carcinoid was established. Postoperative CT showed clear lungs and artificial blood vessels with smooth blood flow (*Figure 1A*). The patient recovered well and was discharged favorably. The patient refused to receive any postoperative therapy except close follow-up. Until 20 months postoperatively, the patient was symptom-free and had no evidences of local and systematic abnormalities.

To explore the underlying mechanisms, a genetic mutation profiling of 295 cancer related genes was performed by NGS (OncoScreenTM 295 genes, Burning Rock Dx, Guangzhou, China, *Figure S1*). The gene sequencing result indicated germline *MEN1* mutation and two somatic mutations on *MEN1* gene (One nonsense mutation in exon 10 with 45.6% frequency and one

 

A

| Gene | Mutation type | Amino acid and base change | Frequency (%) |
|---|---|---|---|
| Germline *MEN1* | Exon 10 T546A missense mutation | p. T546A<br>c. 1636A>G | 50.87 |
| Somatic *MEN1* | Exon 10 G471* nonsense mutation | p. G471*<br>c. 1411G>T | 45.6 |
| Somatic *MEN1* | Exon 6 L288P missense mutation | p. L288P<br>c. 863T>C | 41.9 |

B

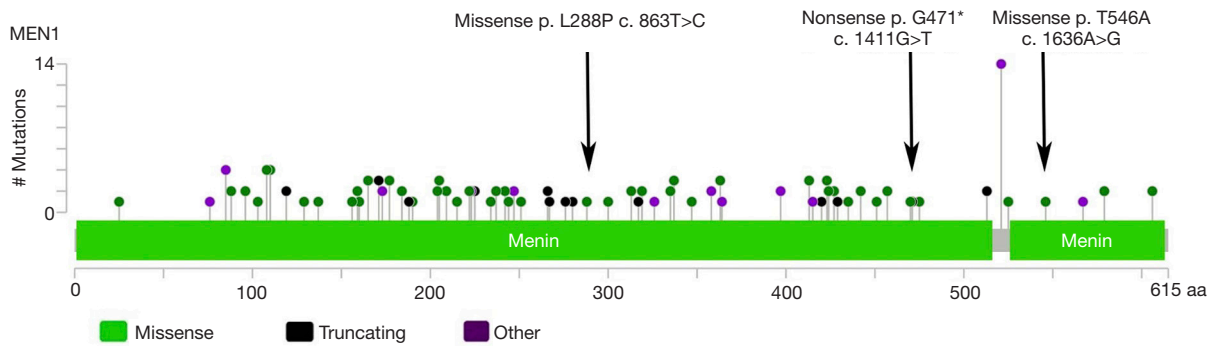


**Figure 2** Gene mutation analysis. (A) NGS analysis detected germline and somatic *MEN1* mutations; (B) MutationMap of *MEN1* mutation from TCGA database. NGS, next generation sequencing; MEN1, multiple endocrine neoplasia type 1; TCGA, the cancer genome atlas.

missense mutation in exon 6 with 41.9% frequency) and no copy number variation or fusion events were detected (*Figure 2A*). We further point out somatic mutation locus of our patient on MutationMap together with all *MEN1* mutations from the cancer genome atlas (TCGA) database (*Figure 2B*). We also retrieved the clinicopathologic characteristics of all thymic carcinoid patients with the initial manifestation of MEN1 syndrome in previous published literatures from PubMed.

## Discussion

*MEN1* gene mutations can be identified in 70–95% of MEN1 patients. MEN1 follows Knudson's "two-hit" model for tumor suppressor gene carcinogenesis. The first hit is a heterozygous *MEN1* germline mutation, and the second hit is a *MEN1* somatic mutation and gives cells the survival advantage needed for tumor development (5). The thymic carcinoid of our case might be caused by the twice mutations on *MEN1* gene according to Knudson's "two-hit" model. Carcinoid tumors are estimated to occur in about 10% of MEN1 patients, and thymic carcinoids were reported be more aggressive with a poor prognosis of 10-year overall survival rate about 25–36% in the literature (4). Thymic carcinoids are more prevalent in males than in females and most patients are clinically silent.

In literature, we found six patients exhibited thymic carcinoid as the initial manifestation of MEN1 syndrome (4,6-10). We summarized the clinical features of these cases (*Table 1*). We confirmed that a higher percentage of thymic carcinoids can occur in men which might the effect of sex hormone promoting the proliferation and maturation of thymocyte in MEN1 syndrome (*Table 1*) (11). The age of patients was young, ranging from 23 to 53 with a median age is 36.5, which might indicate the aggressive nature of disease. Gibril *et al.* reported that about 1/3 MEN1 related thymic carcinoid patients were asymptomatic or only have non-specific symptoms when they had already local invasion or metastases at the time of initial diagnosis (12). The mutations of *MEN1* are also listed in the *Table 1*. The types of mutations include duplication, insertion, deletion, frameshift and nonsense mutation, which occur in exon 2, 3, 5, 9 and 10. Among all the mutations, the mutations in exon10 occur three times which is the same for our case.

Although MEN1 related thymic carcinoid patients only account for less than 5 percentage of all the MEN1 patients, they were associated with an increased mortality and a poorer prognosis due to the more aggressive nature and potential for metastasis (13-15). Early and correct diagnosis is particularly important for thymic carcinoid patients with

 

**Table 1** Literature review of patients with thymic carcinoid as the initial manifestation of MEN1 syndrome

| Reference | Age/sex | Smoking | Type of *MEN1* mutation | Other organs involvement | Family history of MEN1 | MEN1 syndrome diagnosis | Follow-up (months) | Status |
|---|---|---|---|---|---|---|---|---|
| Christakis *et al.* (4) | 23/M | No | Duplication and insertion mutation of exons 9, 10 | None | NK | Yes | 84 | Dead |
| Hasani-Ranjbar *et al.* (6) | 29/M | No | Deletion mutation exon 10 | PH/PA | Yes | Yes | 24 | Alive |
| Kikuchi *et al.* (7) | 53/M | NK | Deletion mutation exon 5 | Parathyroid tumor/PET | No | Yes | 36 | Alive |
| Ghazi *et al.* (8) | 44/M | NK | Frameshift mutation exon 10 | PA/PH | Yes | Yes | 49 | Dead |
| Ferolla *et al.* (9) | 47/M | Yes | Frameshift mutation exon 2 | PH | Yes | Yes | 36 | Dead |
| Boix *et al.* (10) | 25/F | NK | Nonsense mutation exon 3 | None | Yes | Yes | 111 | Dead |

M, male; F, female; NK, not known; PH, parathyroid hyperplasia; PA, pituitary adenoma; PET, pancreatic endocrine tumor; MEN1, multiple endocrine neoplasia type 1.

MEN1 syndrome. In our case, the patient was diagnosed as thymic atypical carcinoid with mutation of *MEN1* gene. But he had none of other organs involvement at the time of diagnosis and a negative family history of MEN1 syndrome. However, based on the findings of our literature review, we have to bear in mind that this thymic carcinoid patient with *MEN1* somatic mutation might develop metachronous neoplasias.

Therefore, we proposed that gene mutation test of *MEN1* and evaluation of other organs are recommended for thymic carcinoid patients. Moreover, close follow-up of thymic carcinoid patients with somatic mutation of *MEN1* gene is necessary and could help detect disease recurrence and metastases early.

## Conclusions

Thymic carcinoid patients with *MEN1* gene mutation are rare. Literature review shows that a much higher percentage of *MEN1* gene mutation related thymic carcinoids can occur in men and develop synchronous or metachronous neoplasia in other organs. Therefore, for patients with thymic carcinoid, testing of *MEN1* gene mutation is recommended. In addition, systematic evaluations and close follow-up are necessary for the thymic carcinoid patients with *MEN1* mutation because of the highly possible involvement of other organs and development of MEN1 syndrome.

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## Footnote

*Conflicts of Interests*: The authors have no conflicts of interest to declare.

*Informed Consent*: The patient granted written informed consent for publication of this manuscript and the accompanying images.

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**Supplementary**

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|---|---|---|---|---|---|---|---|---|---|
| ABL1 | BRAF | CHEK2 | ETV4 | FGFR4 | JAK2 | MRE11A | PALB2 | RAD51D | STAG2 |
| AKT1 | BRCA1 | CHUK | ETV5 | FLT1 | JAK3 | MSH2 | PARP1 | RAD52 | STAT4 |
| AKT2 | BRCA2 | CIC | ETV6 | FLT3 | JUN | MSH6 | PARP2 | RAD54L | STK11 |
| AKT3 | BRIP1 | CRBN | EWSR1 | FLT4 | KDM5A | MTOR | PARP3 | RAF1 | SUFU |
| ALK | BTG1 | CREBBP | EZH2 | FOXL2 | KDM5C | MUTYH | PARP4 | RARA | SYK |
| ALOX12B | BTK | CRKL | FAM123B | GATA1 | KDM6A | MYC | PAX5 | RB1 | TBX3 |
| APC | C11ORF30 | CRLF2 | FAM46C | GATA2 | KDR | MYCL1 | PBRM1 | REL | TET2 |
| APCDD1 | C17ORF39 | CSF1R | FANCA | GATA3 | KEAP1 | MYCN | PDGFRA | RET | TGFBR2 |
| AR | CARD11 | CTCF | FANCC | GNA11 | KIT | MYD88 | PDGFRB | RICTOR | TIPARP |
| ARAF | CASP8 | CTNNA1 | FANCD2 | GNA13 | KLHL6 | MYST3 | PDK1 | RNF43 | TMPRSS2 |
| ARFRP1 | CBFB | CTNNB1 | FANCE | GNAQ | KRAS | NBN | PIK3C2G | RPA1 | TNFAIP3 |
| ARID1A | CBL | CUL4A | FANCF | GNAS | LMO1 | NCOR1 | PIK3C3 | RPTOR | TNFRSF14 |
| ARID2 | CCND1 | CUL4B | FANCG | GPR124 | LRP1B | NF1 | PIK3CA | ROS1 | TOP1 |
| ASXL1 | CCND2 | CYP17A1 | FANCI | GRIN2A | MAP2K1 | NF2 | PIK3CG | RUNX1 | TP53 |
| ATM | CCND3 | DAXX | FANCL | GSK3B | MAP2K2 | NFE2L2 | PIK3R1 | RUNX1T1 | TRRAP |
| ATR | CCNE1 | DDR2 | FANCM | HGF | MAP2K4 | NFKBIA | PIK3R2 | SETD2 | TSC1 |
| ATRX | CD79A | DIS3 | FAT3 | HLA-A | MAP3K1 | NKX2-1 | PMS2 | SF3B1 | TSC2 |
| AURKA | CD79B | DNMT3A | FBXW7 | HRAS | MAP3K13 | NOTCH1 | PNRC1 | SH2B3 | TSHR |
| AURKB | CDC73 | DOT1L | FGF10 | IDH1 | MCL1 | NOTCH2 | PPP2R1A | SMAD2 | VHL |
| AXL | CDH1 | EGFR | FGF12 | IDH2 | MDM2 | NOTCH3 | PRDM1 | SMAD4 | WISP3 |
| BACH1 | CDK12 | EP300 | FGF14 | IGF1 | MDM4 | NOTCH4 | PRKAR1A | SMARCA4 | WT1 |
| BAP1 | CDK4 | EPHA3 | FGF19 | IGF1R | MED12 | NPM1 | PRKDC | SMARCB1 | XPO1 |
| BARD1 | CDK6 | EPHA5 | FGF23 | IGF2 | MEF2B | NRAS | PRSS8 | SMARCD1 | XRCC3 |
| BCL2 | CDK8 | EPHB1 | FGF3 | IKBKE | MEN1 | NSD1 | PTCH1 | SMO | ZNF217 |
| BCL2L2 | CDKN1B | ERBB2 | FGF4 | IKZF1 | MET | NTRK1 | PTEN | SOCS1 | ZNF703 |
| BCL6 | CDKN2A | ERBB3 | FGF6 | IL7R | MITF | NTRK2 | PTPN11 | SOX10 | |
| BCOR | CDKN2B | ERBB4 | FGF7 | INHBA | MLH1 | NTRK3 | RAD50 | SOX2 | |
| BCORL1 | CDKN2C | ERG | FGFR1 | IRF4 | MLL | NUP93 | RAD51 | SPEN | |
| BCR | CEBPA | ESR1 | FGFR2 | IRS2 | MLL2 | PAK3 | RAD51B | SPOP | |
| BLM | CHEK1 | ETV1 | FGFR3 | JAK1 | MPL | PAK7 | RAD51C | SRC | |


**Figure S1** Next generation sequencing on the mutations of 295 tumor-related genes.