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CASE REPORT

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Successful management of a multiple endocrine neoplasia type 1-associated thymic neuroendocrine neoplasms with acute chest pain as initial symptom: A rare case report

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Key Clinical Message

Acute chest pain can be the first manifestation of multiple endocrine neoplasia type 1(MEN1)-associated thymic neuroendocrine neoplasms (NEN). Comprehensive treatment may be an effective strategy for MEN1-associated NEN.

Abstract

Multiple endocrine neoplasia type 1(MEN1)-associated thymic neuroendocrine neoplasms (NEN) is caused by the mutation of tumor suppressor *MEN1* gene. Patients with MEN1-associated NEN initially presenting with acute chest pain are very rare. In the manuscript, we reported a case of a 45-year-old man who developed MEN1-associated NEN with acute chest pain as initial symptom. Thoracoscopic thymotomy was performed and thymic NEN was successfully removed. Genetic test showed a germline mutation of *MEN1* gene in this patient. Immunohistochemical staining exhibited Syn(+), CgA(+), INSM1(+), CD56(+) and Ki67-positive cells (2%) in MEN1-associated NEN. Further evaluation unveiled MEN1-associated benign tumors including digestive NEN and pituitary gland adenoma. The 99mTc-HYNIC-TOC scintigraphy showed that focally increased radioactivity in the mid-upper abdomen. This patient was administered with 50Gy/25F of radiation dose to treat the postoperative lesions. Subsequently, sandostatin LAR (30 mg per week) was used as systemic therapy. He had no recurrence or metastasis for 6-month follow-up. Thus, acute chest pain can be the first manifestation of MEN1-associated NEN, and comprehensive treatment including surgery, radiation and systemic treatment may be an effective strategy for MEN1-associated NEN.

KEYWORDS

chest pain, multiple endocrine neoplasia type 1, thymic neuroendocrine neoplasms, treatment

1 | INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disease with a prevalence of about 2/100,000, characterized by several benign and malignant tumors including parathyroid gland tumors, pituitary tumors, enteropancreatic endocrine cell tumors and thymic neuroendocrine tumors.[1] Thymic neuroendocrine neoplasms (NEN), which are the most common cause of anterior mediastinal mass in patients with MEN1, occurs in 2%–8% of MEN1 patients.[2] Thymic NEN usually exhibited nonfunctional and aggressive hallmarks, with the metastases of mediastinal lymph nodes in approximately 50% of patients at diagnosis. Approximately 150 cases of thymic NEN have been described in the literature, highlighting very rare nature of this tumor, while it has an association with MEN1.[3] The vast majority of MEN1-associated thymic NEN cases are male despite autosomal dominant pattern of inheritance, and almost all patients have a history of smoking.[4] The menin protein, a tumor suppressor coded by *MEN1* gene, plays a crucial role in hindering tumor development. More than 1000 pathogenic variants of *MEN1* have been identified that disrupted the function of menin, leading to loss of tumor suppressive ability.[5]

About one-third of patients with thymic NEN have no symptoms and thymic NEN will be found by chance due to unrelated disease or MEN1 monitoring.[6] However, MEN1-associated thymic NEN initially presenting with acute chest pain has been never described. Herein, we reported an extremely rare case of a 45-year-old man with a diagnosis of MEN1-associated thymic NEN with acute chest pain who was treated with surgical, radiation and systemic therapies.

2 | CASE HISTORY/EXAMINATION

A 45-year-old man admitted for hospitalization with complaints of severe and intense chest pain that had lasted for 2 h. The patient's chest pain was located behind the sternum and was not relieved by oral nitroglycerin. He had no associated nausea, vomiting, diaphoresis, or abdominal pain.

He denied coronary artery disease. He had a history of parathyroidectomy due to primary hyperparathyroidism 8 years ago. Besides, this patient's history revealed hypergastrinemia, gastroesophageal reflux, gastric and duodenal mass, abdominal mass and hypercortisolism. There was no family history of specific illnesses. On physical examination, his body temperature was 36.5°C, respiratory rate of 17 breaths per minute, blood pressure of 121/70 mmHg, and heart rate of 89 bpm.

3 | INVESTIGATIONS

Next, we performed a series of accessory examinations to comprehensively evaluate the condition of this patient. Electrocardiography (ECG), myocardial enzymology and D-dimer concentration were normal. Chest computed tomography (CT) revealed a large mass in the right anterior mediastinum with invasion into adjacent pericardium and right mediastinal pleura (Figure 1a). CT of the aorta uncovered that the mass lesion was heterogeneously enhanced (Figure 1b–d). Thoracoscopic thymotomy was performed and thymic mass was successfully removed. The histopathologic analysis diagnosed the mass as a thymic NEN and immunohistochemical staining exhibited the expression of Syn, CgA, INSM1, CD56, and Ki67(2%) were positive (Figures 2A and 3). After surgery, the patient's chest pain was relieved. Based on medical history and pathological results, we suspected that he suffered from MEN1. The whole-exome sequencing unveiled a germline c.1072G > T *MEN1* mutation (Figure 4a). 99mTc-HYNIC-TOC scintigraphy showed that focally increased activity in the mid-upper abdomen (Figure 4b). Nodulated bulges were obviously observed in the surface of gastric and duodenum by gastroscopy with the histological diagnosis of

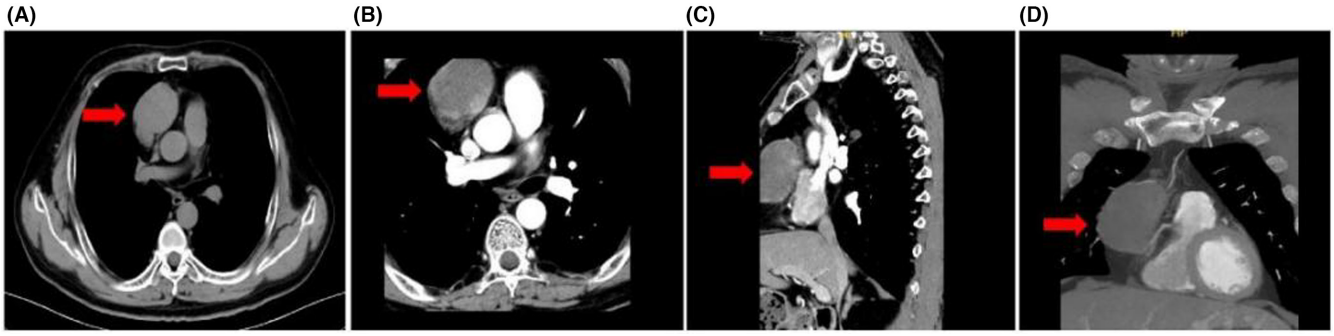

FIGURE 1 CT of thymus mass. (A) A large mass in the right anterior mediastinum (5.6 cm × 4.2 cm × 7.6 cm). (B–D) Heterogeneously enhanced thymus mass in axial, sagittal, and coronal view, respectively.

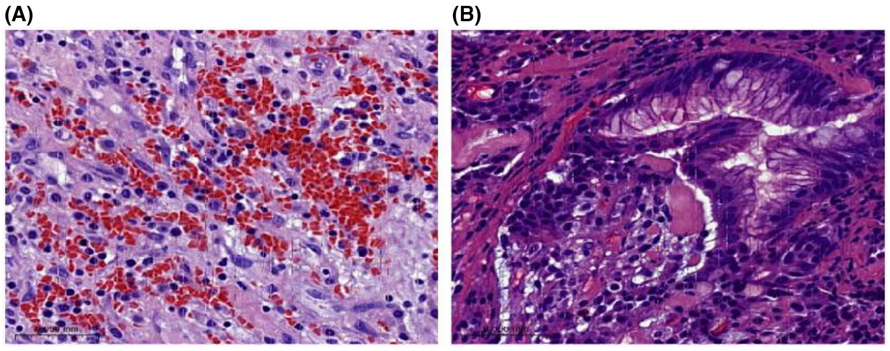

FIGURE 2 Histology of tumor tissues. (A) Thymic NEN (hematoxylin–eosin ×400). (B) Gastric NEN (hematoxylin–eosin ×400).

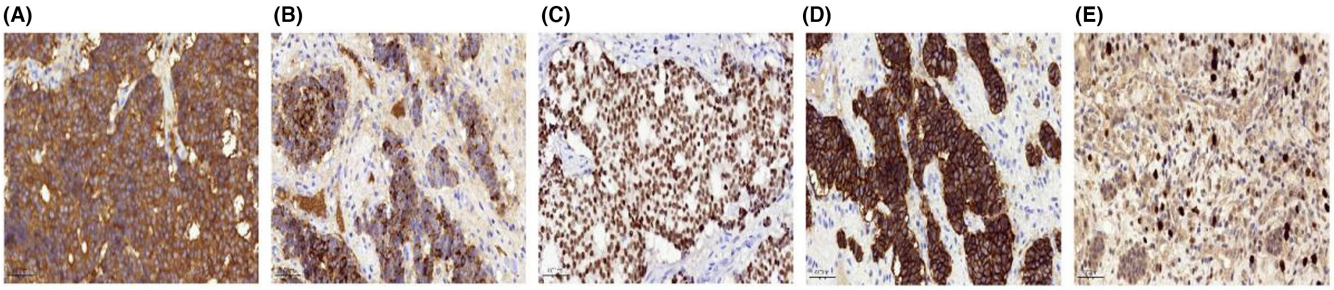

FIGURE 3 Immunohistochemical staining of the thymic NEN (magnification, ×400). The tumor tissues were positive for Syn (A), CgA (B), INSM1 (C), CD56 (d) and Ki67 (E).

NEN grade G1 (Figures 2b and 4c,d). We performed a sella CT rather that magnetic resonance imaging (MRI) because this patient previously had metal crowns of teeth, and CT revealed a pituitary gland adenoma (Figure 4e). A small pancreatic tumor with a diameter of about 7 mm was observed by MRI (Figure 5). He had no Whipple's triad (symptoms of episodic hypoglycemia, plasma glucose concentration <2.8 mmol/L at onset, symptoms disappear immediately after glucose administration). The levels of C-peptide and insulin were normal and the starvation test was negative. We conducted the comprehensively hormonal examinations related to MEN1 (Table 1). This patient was diagnosis as MEN1-associated NEN, but it needs to be differentiated from acute coronary syndrome, pulmonary embolism and aortic dissection.

4 | TREATMENT

This patient was received radiotherapy with a dosage of 50Gy/25F five times a week. Later, we gave this patient sandostatin LAR (30 mg per week) as systemic treatment.

5 | CONCLUSION AND RESULTS

He had no recurrence or metastasis for 6-month follow-up. Acute chest pain can be the first manifestation of MEN1-associated NEN, and comprehensive therapy including surgery, radiation and systemic treatment may be an effective strategy for MEN1-associated NEN.

6 | DISCUSSION

The clinical diagnosis of MEN1 can be established if a patient has one of two conditions: (1) at least two types of MEN1-associated tumors, (2) one MEN1-associated tumor and a relative with a diagnosis of MEN1. Besides, germline *MEN1* mutation indicated by genetic screening is informative to confirm the clinical diagnosis. This patient was definitely diagnosed as MEN1 according to both clinical and molecular criteria. Although thymus NEN is rare, it is a critical cause of complications and death in the MEN1 family because its malignant potential is higher than that of other MEN1-related tumors. Importantly, MEN1-associated thymus NEN leads to poor prognosis owing to its more malignant nature and metastasis hallmark even after radical resection.[7]

There is not enough evidence to determine the best therapeutic strategy for MEN1-associated NEN patients, but complete surgical resection is preferred if possible. A retrospective study included 254 patients found that the median survival of patients treated with surgery was significantly longer than that of patients who were not treated with surgery.[8] Besides, it is recommended that prophylactic thymotomy should be performed when parathyroid resection was done, which may reduce the

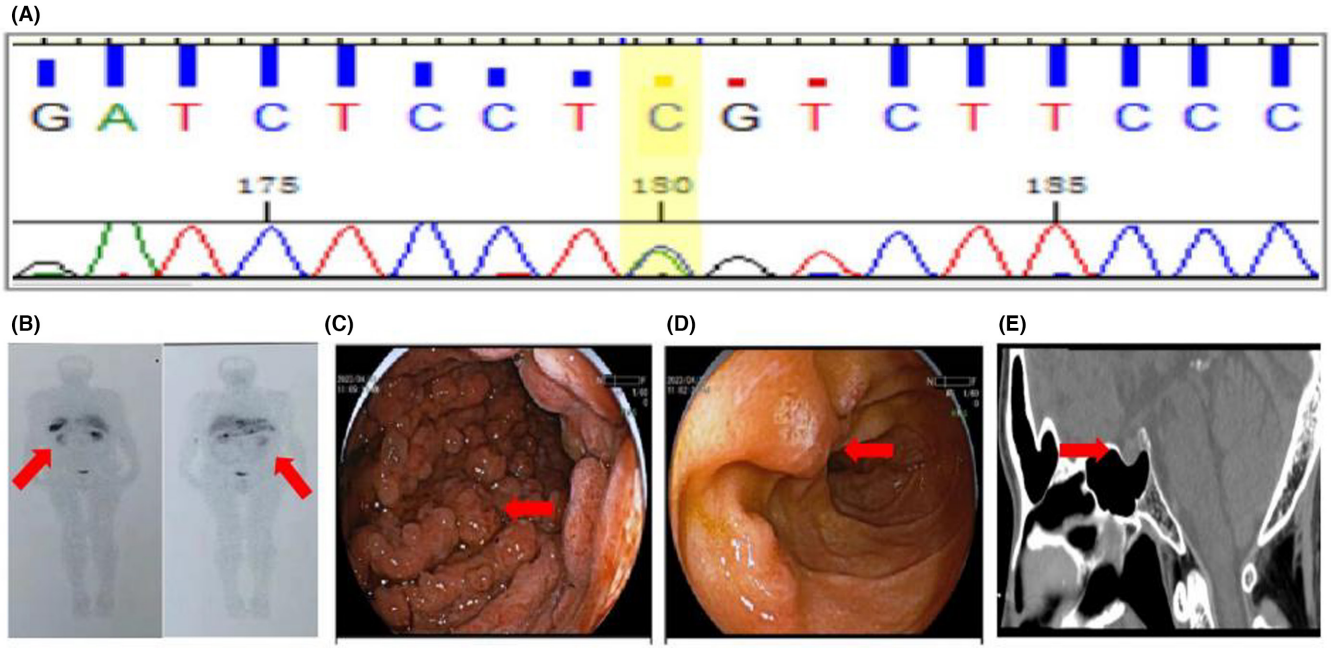

FIGURE 4 Molecular and clinical diagnosis of MEN1. (A) Map of the sanger sequencing peaks. (B) Increased activity in the mid-upper abdomen by 99mTc-HYNIC-TOC scintigraphy. (C) Nodulated bulges of the surface of gastric by gastroscopy. (D) Nodulated bulges of the surface of duodenumby by gastroscopy. (E) Pituitary gland adenoma (11 mm × 15 mm × 9 mm) by sella CT.

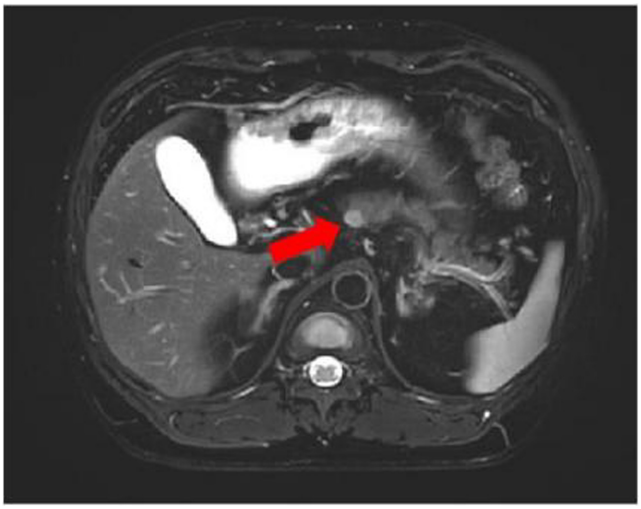

FIGURE 5 MRI without contrast of the abdomen revealed a small nodular signal of pancreatic body with 7 mm in diameter.

risk of developing a thymus NEN. Evidence supporting the benefits of adjuvant or radiotherapy after surgery is limited and controversial. In a study included 12 patients who had been resected for thymic NEN, three patients received adjuvant radiotherapy without recurrence.[9] A non-randomized study showed that those who received adjuvant or radical radiotherapy had poor outcomes.[10] While somatostatin analogues (SAA) exerted suppressive effect on tumor growth in NEN, their potential anti-tumor efficacy in thymic NEN remained uncertain.[4] National Comprehensive Cancer Network (NCCN) guidelines recommend that octreotide can be used as first-line therapy for patients with local unresectable or distant metastases lesions. However, SAA as first-line therapy exhibited an objective response rate (ORR) of no more than 10%.[11] In addition, a study suggested that everolimus, an inhibitor of mammalian target of rapamycin (mTOR), is an effective and promising treatment for thymic NEN.[12] Of note, Ma et al revealed that dihydroorotate dehydrogenase (DHODH) is target for MEN1-mutated tumor cells, and leflunomide, an inhibitor of DHODH, can efficiently impede the growth of MEN1-mutated tumors. Moreover, leflunomide exhibited the ability to induce stable disease (SD) in advanced-stage tumors that progressed following first-line treatments, suggesting it could offer a safer and more viable option for patients with MEN1.[13]

Somatostatin receptor (SSTR) expression is critical for the effective treatment of well-differentiated NEN with SSA.[14] Unfortunately, the staining of the thymic mass was negative for SSTR in this patient. However, due to heterogeneity hallmarks of cancer cells that universally existed in the tumor, inadequate biopsy specimens may not demonstrated that the entire tumor tissue is positive for SSTR. Inspiringly, the patient after octreotide in combination with radiation treatment had no recurrence or metastasis for 6-month follow-up. Strikingly, a prospective study found that patients with nonfunctioning pancreatic endocrine carcinomas (NF-PEC) were received octreotide

TABLE 1 Hormonal data of this patient.

Parameter	Reference	Value
PRL (uIU/mL)	86–324	337
LH (IU/L)	1.7–8.6	10.9
FSH (IU/L)	1.5–12.4	13.3
ACTH (ng/L) 8 AM	7.2–63.3	48.3
Cortisol (nmol/L) 8 am	133–537	309
Cortisol free (ug/dL) 24-h urine	–	57
GH (ng/ml)	≤2.5	0.6
IGF-1 (ng/mL)	80.6–229	214
TSH (μIU/mL)	0.3–4.2	1.8
TT3 (nmol/L)	1.3–3.1	1.2
TT4 (nmol/L)	66–181	59.7
FT3 (pmol/L)	3.1–6.8	4.2
FT4 (pmol/L)	12–22	19.1
PTH (ng/L)	15–65	39.9
Insulin (μU/mL)	2.6–24.9	17.9
C-peptide (ng/mL)	1.1–4.4	4.4
Gastrin-17 (pmol/L)	1–15	>40
Angiotensin II (pg/mL) Supine position	25–129	82.2
Aldosterone (pg/mL) Supine position	10–160	68.8
Plasma renin activity (pg/mL) Supine position	4–24	15.7
ARR	0–38	4.4
Plasma free NMN (pg/mL)	52.7	<145
Plasma free MN (pg/mL)	60.6	<62
plasma free NMN + MN(pg/mL)	113.3	<207

Abbreviations: ARR, Ratio of aldosterone-to-renin activity; FT3, free serum triiodothyronine; FT4, free serum tetraiodothyronine; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor-1; MN, metanephrine; NMN, normetanephrine; LH, luteinizing hormone; PRL, prolactin; PTH, parathyroid hormone; TT3, total serum triiodothyronine; TSH, thyroid stimulating hormone; TT4, total serum tetraiodothyronine.

and there is no difference in the expression of SSTR2 and SSTR5 between NF-PEC that remained stable and those that progressed, suggesting that SSTR2 and SSTR5 expression may have no association with response to therapy.[15] We might hypothesize that octreotide may exert underlying effect in SSTR-negative nonfunctioning thymic NEN and a series of researches may be explored in the future.

AUTHOR CONTRIBUTIONS

Xuesong Li: Resources; visualization; writing – original draft; writing – review and editing. **Liangbiao Gu:** Data curation; investigation; validation. **Wenhui Zhao:** Methodology. **Zhuo Yu:** Conceptualization. **Jianzhong Xiao:** Project administration. **Chenxiang Cao:** Funding acquisition.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study can be available for review upon reasonable request.

ETHICS STATEMENT

This article is a practice-oriented case study description that made extensive use of secondary information sources and also drew upon the professional knowledge of the co-authors. As such, the creation of this case study article did not involve any formal research study, nor did it involve human participation in a research study. As such, IRB review was not required for this article.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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