

Atypical Thymic Carcinoid in a Patient with Zollinger-Ellison Syndrome

Jiyun Lee, M.D.¹, Kwanyong Hyun, M.D.¹, Mi Hyoung Moon, M.D.¹, Seok Whan Moon, M.D.¹, Jae Kil Park, M.D.¹, Si Young Choi, M.D.², Young Jo Sa, M.D.³, Kyung Soo Kim, M.D.¹

¹Department of Thoracic and Cardiovascular Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea; ²Department of Thoracic and Cardiovascular Surgery, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea; ³Department of Thoracic and Cardiovascular Surgery, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Atypical thymic carcinoid is an extremely rare tumor with a poor prognosis. In addition to its known association with multiple endocrine neoplasia type 1, its hallmark characteristics include local invasion and early distant metastasis. In this report, we share our experience treating atypical thymic carcinoid in a patient with Zollinger-Ellison syndrome.

Key words: 1. Zollinger-Ellison syndrome
2. Carcinoid tumor
3. Neuroendocrine tumors
4. Multiple endocrine neoplasia type 1

Case report

A 57-year-old man presented to emergency department of Seoul St. Mary's Hospital with chest discomfort. Although the patient complained only of chest discomfort at the time of presentation, close questioning revealed him to have radiating pain to the neck, back, and both shoulders. In addition, he had a history of uncontrolled hypertension, with a systolic blood pressure reading as high as 180–220 mm Hg 1 day prior. The patient's social history was notable for prior tobacco use of about 10 pack-years, and he had quit smoking approximately 10 years prior to presentation. He had a past medical history of Zollinger-Ellison syndrome (ZES). In the past, the patient also suffered from multiple recurrent duodenal

ulcers, which were refractory to medical treatment with a proton pump inhibitor (30 mg of lansoprazole once daily). Nine years prior to his presentation, he underwent small bowel segmental resection for a perforated ulcer 30 cm distal to the ligament of Treitz. The patient had no other history of past or current medical illness.

The patient's blood studies were unremarkable, including a serum blood urea nitrogen level of 15.4 mg/dL (reference range, 7.0–20.0 mg/dL), a creatinine level of 0.80 mg/dL (reference range, 0.6–1.2 mg/dL), a glucose level of 136 mg/dL (reference range, 50–100 mg/dL), a calcium level of 10.1 mg/dL (reference range, 8.0–10.0 mg/dL), a potassium level of 4.7 mEq/L (reference range, 3.5–5.1 mEq/L), a creatine phosphokinase level of 35 U/L (reference

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Corresponding author: Kyung Soo Kim, Department of Thoracic and Cardiovascular Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea (Tel) 82-2-2258-2858 (Fax) 82-2-594-8644 (E-mail) cskks@catholic.ac.kr

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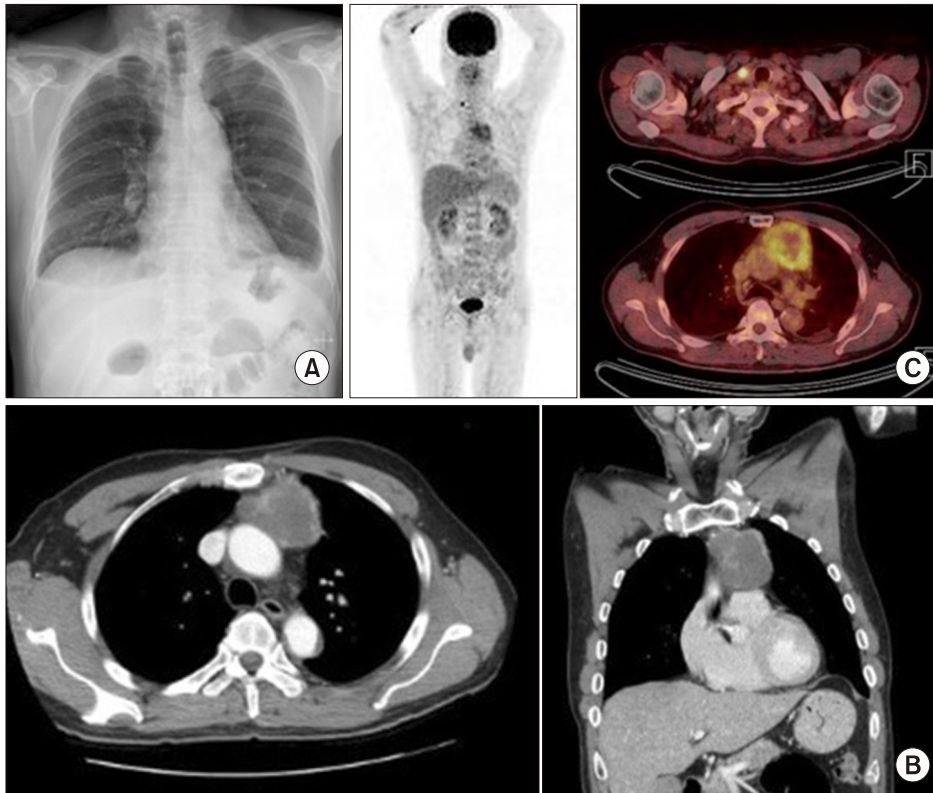


Fig. 1. Imaging studies of the chest. (A) A plain chest X-ray showed a widened mediastinum. (B) A 6.2-cm mass in the anterior mediastinum detected by computed tomography. (C) Positron emission tomography-computed tomography confirmed intensified uptake by the mass within the mediastinum and by the right lobe of the thyroid.

range, 26–200 U/L), and a bicarbonate level of 24.5 mmol/L (reference range, 21–28 mmol/L). In addition, tests of thyroid function produced no abnormal findings; the results of these tests included a triiodothyronine level of 1.03 ng/mL (reference range, 0.6–1.81 ng/mL), a thyroxine (T_4) level of 8.3 $\mu\text{g/dL}$ (reference range, 3.2–12.6 $\mu\text{g/dL}$), a free T_4 level of 1.13 ng/dL (reference range, 0.82–1.76 ng/dL), and a thyroid-stimulating hormone (TSH) level of 2.973 $\mu\text{IU/mL}$ (reference range, 0.55–4.78 $\mu\text{IU/mL}$). The level of serum gastrin was found to be 315.0 mg/L (reference range, 0–108 mg/L).

Abdominal-pelvic computed tomography (CT) also yielded no abnormal findings. However, a plain chest X-ray showed a widened mediastinum. Further imaging with chest CT revealed a 6.2-cm, heterogeneously dense mass in the anterior mediastinum, and this mass appeared to be of thymic origin. Positron emission tomography-CT (PET-CT) confirmed intensified uptake by the mass within the mediastinum (maximum standardized uptake value, 5.4) and by the right lobe of the thyroid (Fig. 1). Ultrasound-guided fine-needle aspiration of the thyroid gland demonstrated the

presence of papillary carcinoma, and the patient elected to undergo surgical treatment for thyroid cancer separately.

Since imaging revealed no apparent local invasion, video-assisted thoracoscopic surgery (VATS) was used to resect the mediastinal mass. Importantly, the size of the mass meant that it was borderline in terms of whether VATS was recommended. The operation was performed under 1-lung ventilation using a left-sided 3-port VATS approach. Since carbon dioxide (CO_2) insufflation under low pressure does not have adverse hemodynamic effects and allows for a sufficient view of the surgical field, CO_2 insufflation combined with one-lung ventilation was utilized, and thymectomy was performed to remove the indigenous tumor and attached fat en bloc. Dense adhesions involving the pericardium, ascending aortic abutment, and innominate vein were present, requiring careful dissection. The perithymic, prevascular, and para-aortic lymph nodes were also removed at the time of the procedure (Fig. 2). The specimens were placed in an Endo Bag (Medtronic, Minneapolis, MN, USA) for eventual thoracic extraction through an extended

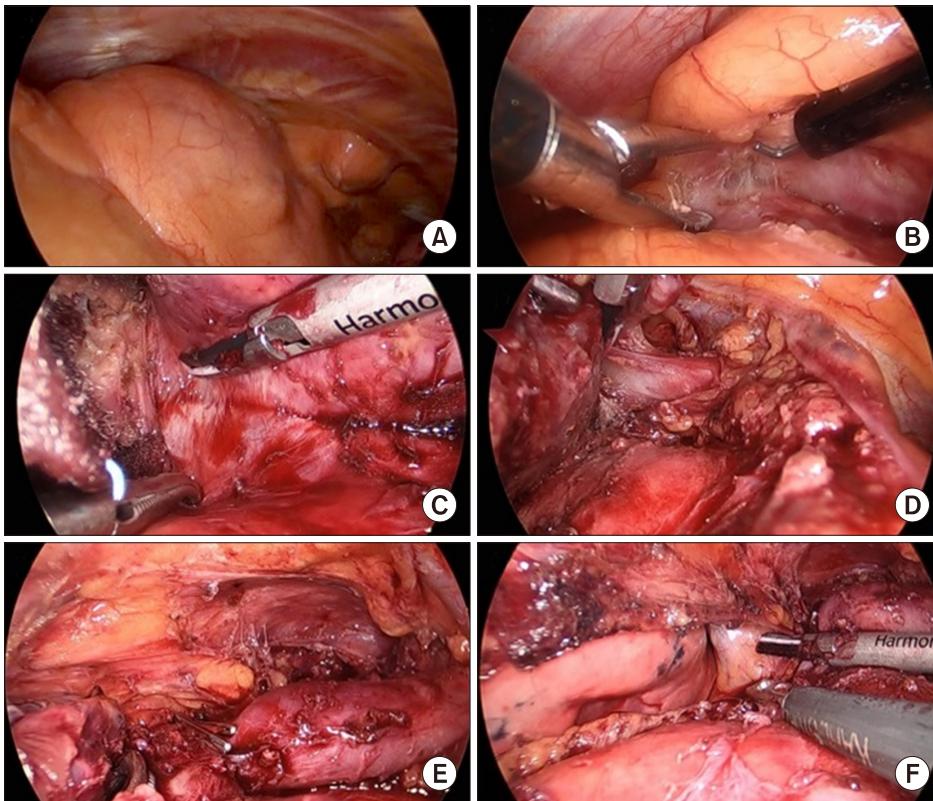


Fig. 2. Thoracoscopic findings. (A) A protuberant mass in the anterior mediastinum. (B) Dissection at the base of the tumor, above the pericardium. (C) Dense adhesions between the mass and the pericardium. (D) Dissection of the mass around the innominate vein to the upper pole of the thymus. (E) Complete resection of the mediastinal tumor, including the perithymic fat, preserving the innominate vein. (F) The contralateral pleural cavity as seen through a defect in the right-sided mediastinal pleura, which was resected with the mass.

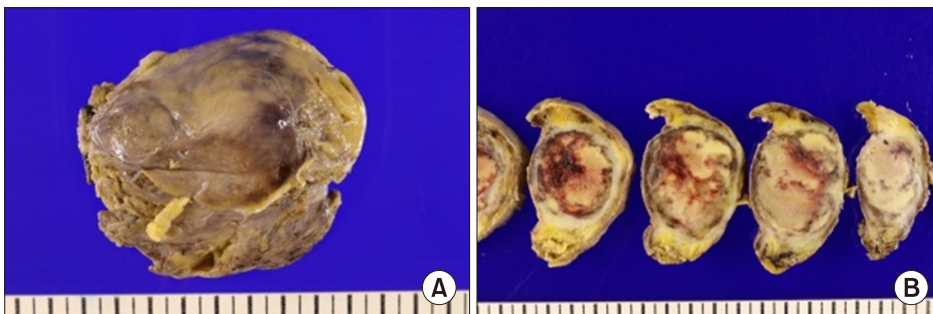


Fig. 3. (A, B) Gross appearance of the completely resected mediastinal mass (6.0×4.7×3.8 cm), confirmed to be an atypical thymic carcinoid.

fifth intercostal port incision. A single 24F tube was placed in the chest cavity, followed by routine closure of all incisions. The estimated blood loss during the 230-minute procedure was 150 mL. The patient's hospital course was uneventful, and he was discharged on postoperative day 6.

The excised tumor, later diagnosed as an atypical thymic carcinoid, was irregularly shaped, but encapsulated, and measured 6.0×4.7×3.8 cm (Fig. 3). The resected margins of the excised tumor were clear, and there was no evidence of local invasion or nodal metastasis (0/9). Much of the mass (80%) was dege-

nerative, showing multifocal necrotic changes. However, mitotic activity was not inordinate (high-power fields, 0–10/10). The immunohistochemical stains were positive for CD56, chromogranin A, neuron-specific enolase (NSE), and synaptophysin, suggestive of a neuroendocrine tumor. The Ki-67 proliferative index was low (5%), and thyroid transcription factor 1 was absent.

After a multidisciplinary deliberation focused on the often aggressive nature of atypical thymic carcinoid tumors, adjuvant radiotherapy was administered at 55–60 Gy. The patient visited the outpatient clinic

every 6 months and remained recurrence-free during 18 months of follow-up. There was no recurrence of clinical symptoms associated with atypical thymic carcinoid after surgery. Tissue from the patient was sent for genetic testing, upon which the multiple endocrine neoplasia type 1 (MEN-1) genetic mutation was detected. After follow-up for 1 year, total thyroidectomy and total parathyroidectomy with autotransplantation were conducted for treatment of concurrent papillary thyroid cancer. Blood studies from the last clinic visit showed a serum free T₄ level of 1.09 ng/dL, a TSH level of 2.514 μ IU/mL, a parathyroid hormone (intact) level of less than 4.6 pg/mL (range, 8.0–76.0 pg/mL), a gastrin level of 329.92 mg/L, and an adrenocorticotropic hormone level of 136.27 pg/mL (range, 10.0–80.0 pg/mL).

This study was reviewed and approved by the Institutional Review Board of Seoul St. Mary's Hospital and informed consent was waived (eIRB no, KC18ZESI0859).

Discussion

Neuroendocrine cells, from which neuroendocrine tumors such as that discussed in our report develop, are diffusely distributed in a variety of organs and tissues. However, the neoplasms they spawn are usually confined to the gastro-entero-hepatic and respiratory systems and seldom involve the mediastinum. Mediastinal growths of this nature may originate from neuroendocrine elements within the thymus itself, from aortopulmonary and paravertebral paragangliomas, from embryonic structures misplaced within the mediastinum, and even from ectopic or supernumerary parathyroid glands; however, thymic neuroendocrine derivation is the most common origin of mediastinal growths [1]. Thymic neuroendocrine tumors can be classified into 4 categories based on their histological features and the degree of malignancy: typical carcinoids, atypical carcinoids, large-cell neuroendocrine tumors, and small-cell neuroendocrine tumors [2].

Thymic carcinoids largely display the following characteristics: (1) low incidence, (2) relatively advanced stage at discovery, (3) tendency to be highly aggressive with a poor prognosis, (4) frequent association with MEN-1, and (5) differing ethnic prevalence, particularly with respect to Caucasians and

Asians. Atypical thymic carcinoids are extremely rare, with an annual incidence of <0.18 per 1,000,000 people. Approximately one-third of patients are asymptomatic. In such cases, disease detection is incidental during routine physical exams and typically occurs at advanced stages. The remaining two-thirds of patients report nonspecific symptoms, primarily cough, chest pain, breathing difficulties, and other afflictions imposed by space-occupying lesions.

The clinical course of thymic carcinoids tends to be aggressive, given the predisposition of these tumors for local recurrence and rather early distant metastasis (20%–30%). In 20%–40% of patients, the tumors invade the chest wall, lung, liver, brain, or other organs. Up to 25% of thymic carcinoids are clearly associated with MEN-1, whereas 2%–8% of patients with MEN-1 develop thymic carcinoids. Thymic carcinoids linked to MEN-1 carry a higher mortality risk than bronchopulmonary carcinoids [3], underscoring a need for periodic thoracic screening via CT with contrast. Although imaging studies lack diagnostic specificity in this setting, chest CT with contrast is the initial imaging modality of choice. Magnetic resonance imaging may also be helpful, if clinically indicated, but PET-CT is considered optional. Ultimately, the diagnosis of an atypical thymic carcinoid relies heavily on immunohistochemical findings. Specifically, this diagnosis involves a positive finding for at least 2 of 4 neuroendocrine markers—chromogranin A, synaptophysin, CD56, and NSE—in more than 50% of tumor cells. The Ki-67 index is obtained to gauge high- or low-level malignancy [2,4].

In approximately 20% of cases, ZES is associated with MEN-1. ZES is an endocrinopathy marked by excessive gastrin secretion and hypertrophic gastric rugae causing multiple treatment-refractory and recurrent peptic ulcers in the distal duodenum and proximal jejunum. In patients with MEN-1 and ZES, common complaints include abdominal pain, weight loss, and a history of renal colic and nephrolithiasis. In approximately 50% of patients, hyperparathyroidism is diagnosed after establishing the presence of ZES. Thus, any patient diagnosed with ZES should be screened for MEN-1 [5].

At present, the only curative treatment for resectable atypical thymic carcinoids is complete surgical excision, and overall survival appears to be longer in cases of R0 resections than in cases without such

resection. A study conducted by Rea et al. [6] found that the long-term survival rate of patients with complete resection was 81.8%, while that of patients without complete resection was only 9.1%. Despite its questionable utility, postoperative radiotherapy, with or without chemotherapy, is often pursued in patients with incompletely resected carcinoids [2,7].

Our case described a patient who presented with an atypical thymic carcinoid years after the diagnosis and treatment of ZES. In highly selective cases, VATS can be considered for the complete resection of thymic carcinoids. Although such tumors are exceedingly rare, the clear predisposition to MEN-1 in patients with documented ZES warrants careful systemic evaluation and long-term surveillance for the potential development of other neuroendocrine tumors.

Conflict of interest

The authors declare that they have no competing interests.

ORCID

Jiyun Lee: <https://orcid.org/0000-0002-4554-9676>
Kwanyong Hyun: <https://orcid.org/0000-0002-2103-3122>
Mi Hyoung Moon: <https://orcid.org/0000-0003-2799-4570>
Seok Whan Moon: <https://orcid.org/0000-0003-3348-6011>

Jae Kil Park: <https://orcid.org/0000-0002-4953-1473>
Si Young Choi: <https://orcid.org/0000-0002-7372-6959>
Young Jo Sa: <https://orcid.org/0000-0002-5806-3640>
Kyung Soo Kim: <https://orcid.org/0000-0002-3680-9851>

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