Increased carbohydrate antigen 19-9 expression in a thymic neuroendocrine tumor

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Abstract
Here, we report a case of carbohydrate antigen (CA) 19-9-producing mediastinal neuroendocrine tumor (NET) (atypical carcinoid). A 54-year-old woman with no specific relevant medical history was referred to our hospital because of increased CA19-9 (95.3 U/ml) detected on health screening. Chest computed tomography (CT) revealed an anterior mediastinal mass without localized lymphadenopathy. Thoracic surgery was performed and the histopathological diagnosis was thymic CA19-9-positive NET. The patient developed mediastinal lymph node metastasis at 1 year (CA19-9: 413 U/ml) and multiple bone metastases 4 years (CA19-9: 2303 U/ml) after surgery. Increased CA19-9 levels paralleled the clinical courses of relapse. To our knowledge, this is the first report of CA19-9-producing thymic NET.

KEYWORDS
immunohistochemical stain, neuroendocrine tumor, thymic carcinoid, tumor marker

INTRODUCTION
Serum level of the tumor-associated carbohydrate biomarker, carbohydrate antigen 19-9 (CA19-9), is used for diagnosis and post-treatment monitoring in patients with pancreatic and gastrointestinal malignancies, with median sensitivity and specificity of 79% (70%–90%) and 82% (68%–91%), respectively, for diagnosis of pancreatic cancer.1,2 Several studies have indicated elevated serum CA19-9 in pancreatic neuroendocrine tumors (NETs).3–7 CA19-9 is important for differentiating between pancreatic adenocarcinomas and pancreatic NETs,6,7 but little is known regarding CA19-9 in other types of NET.

Here, we present a case of CA19-9-producing thymic NET. Elevated CA19-9 was detected incidentally, and subsequent systemic examination revealed an anterior mediastinal mass. Relapse occurred with multiple bone metastases after resection of the mass, and treatment was continued. CA19-9 level was related to the clinical course. We describe the clinical course and a brief review of the relevant literature.

CASE REPORT
A 54-year-old woman with no significant medical history or symptoms was referred to our hospital because of persistently elevated CA19-9 level for 3 months detected on health screening. Physical examinations were unremarkable. Laboratory findings indicated elevated CA19-9 (98.3 U/ml; normal: <37 U/ml), but carcinoembryonic antigen (1.8 ng/dl; normal: <2.5 ng/dl) and cancer antigen 125 (12.8 U/ml; normal: <35 U/ml) were normal. Chest computed tomography (CT) showed an anterior mediastinal mass positive on 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (18-FDG-PET/CT), with no mediastinal lymphadenopathy or distant metastases (Figure 1). There were no abnormal findings on abdominal CT and upper/lower gastrointestinal endoscopy. Thoracoscopy thymectomy and anterior mediastinal lymph node dissection (ND1) were performed. Pathological examination revealed irregularly shaped sheets and nests of tumor cells with rosette-like organoid construction. A diagnosis of NET (atypical carcinoid) was made with Ki-67 labeling index <5.6% (Figure 2).
Mediastinal lymph node enlargement and elevated CA19-9 (413 U/ml) were detected at 1-year follow-up. Mediastinal lymph node dissection was performed by video-assisted thoracic surgery (VATS) and thymic NET metastasis was confirmed. CA19-9 decreased and remained at 345 U/ml for 2 years with no relapse on serial chest CT. However, CA19-9 suddenly increased to 2303 U/ml and lumbago developed 4 years after initial surgery. FDG-PET/CT showed diffuse, multiple FDG uptake in the thoracolumbar spine and iliac-sacrum, femur, and ribs (Figure 3a). Fat-suppressed contrast-enhanced T1-weighted magnetic resonance imaging (MRI) showed heterogeneous infiltration of the vertebra, suggesting multiple bone metastases (Figure 3b). Iliac bone biopsy confirmed metastasis from thymic NET. Everolimus, octreotide long-acting repeatable, and denosumab (RANKL-inhibiting fully human mAb) every 4 weeks was continued for 1 year. CA19-9 level remained almost stable (2040–3160 U/ml) during combination therapy. Tumor cells from the mediastinal lymph node and iliac bone were CA19-9-positive (Figure 2f).

DISCUSSION

CA19-9 production in tumor cells was confirmed immunohistologically and serial changes in CA19-9 paralleled the clinical
course in this case of CA19-9-producing thymic NET (thymic carcinoid). CA19-9 elevation is also observed in other conditions, including biliary obstruction and inflammation, digestive tract inflammation, and other pulmonary malignancies. The mechanism underlying CA19-9 production in NET cells is unclear, and this is the first report of CA19-9-producing thymic NET. PubMed search using the keywords “mediastinal carcinoid,” “thymic neuroendocrine tumor or carcinoid,” “mediastinal tumor,” and “CA19-9” identified no reports in the English literature.

CA19-9 is a diagnostic tumor marker to differentiate between pancreatic adenocarcinoma and NETs. Several studies of CA19-9 in pancreatic NET patients have been reported. Luo et al. reported that CA19-9 > 16 U/ml was significantly associated with a higher proportion of patients at advanced stages and was an adverse prognostic factor for overall survival. Chen et al. reported that serum CA19-9 was elevated in 12.4% (12/112 cases) of pancreatic NETs, and elevated CA19-9 was an independent predictor of NET G3 tumor, suggesting that CA19-9 elevation is associated with high-grade aggressiveness. In medullary thyroid cancer, elevated CA19-9 was predictive of poor prognosis. Therefore, elevated CA19-9 may be a predictor of poor prognosis and aggressive NET. Thymic NET is a rare clinical entity, with poorer prognosis than foregut counterparts and with the potential for local and distant metastasis. In our case, mediastinal lymph node metastasis and multiple bone metastasis were detected 1 and 4 years after initial surgery, respectively. The metastatic potential was consistent with elevated CA19-9 in pancreatic NETs.

Similar thymic NETs with multiple bone metastases have been reported, with frequency ranging between 7% and 15% in NETs. However, somatostatin analog and metaiodobenzylguanidine (octreotide) scintigraphy were used to evaluate bone metastasis and did not focus on thymic NETs. Kobashi et al. reported the usefulness of FDG-PET for detecting bone metastasis in cases of thymic NET. Therefore, we examined the clinical manifestations using multiple modalities in patients with NETs. A sudden increase in CA19-9 indicated bone metastasis in our case. Although there were no significant increases in CA19-9 in our case during treatment with everolimus over 1 year, CA19-9 monitoring may be a useful indicator of the need to switch to other therapies.

In conclusion, we described a case of thymic NET with the development of bone metastasis 4 years after radical thoracotomy. The increase in CA19-9 produced by tumor cells was the initial clinical index for diagnosis, and serial changes in CA19-9 were associated with clinically relevant parameters.
This case suggests that thymic NET has the potential to produce CA19-9.

CONFLICT OF INTEREST
The authors have no potential conflicts of interest associated with this case report.

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REFERENCES
1. Lee T, Teng TZJ, Shelat VG. Carbohydrate antigen 19-9 - tumor marker: past, present, and future. World J Gastrointest Surg. 2020;12:468–90.
2. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. Eur J Surg Oncol. 2007;33:266–70.
3. Luo G, Jin K, Cheng H, Liu C, Guo M, Lu Y, et al. Carbohydrate antigen 19-9 as a prognostic biomarker in pancreatic neuroendocrine tumors. Oncol Lett. 2017;14:6795–800.
4. Chen K, Zhang W, Zhang Z, He Y, Liu Y, Yang X. Simple vascular architecture classification in predicting pancreatic neuroendocrine tumor grade and prognosis. Dig Dis Sci. 2018;63:3147–52.
5. Hijjoka M, Ito T, Igarashi H, Fujimori N, Lee L, Nakamura T, et al. Serum chromogranin A is a useful marker for Japanese patients with pancreatic neuroendocrine tumors. Cancer Sci. 2014;105:1464–71.
6. Zhuge X, Guo C, Chen Y, Feng L, Jia R, Zhao Y, et al. The levels of tumor markers in pancreatic neuroendocrine carcinoma and their values in differentiation between pancreatic neuroendocrine carcinoma and pancreatic ductal adenocarcinoma. Pancreas. 2018;47:1290–5.
7. Karaman K, Bostanci EB, Aksoy E, Kurt M, Celep B, Ulas M, et al. The predictive value of mean platelet volume in differential diagnosis of non-functional pancreatic neuroendocrine tumors from pancreatic adenocarcinomas. Eur J Intern Med. 2011;22:e95–8.
8. Elisei R, Loruso L, Romei C, Bottici V, Mazzeo S, Giani C, et al. Medullary thyroid cancer secreting carbohydrate antigen 19-9 (Ca 19-9): a fatal case report. J Clin Endocrinol Metab. 2013;98:3550–4.
9. Elisei R, Loruso L, Piaggi P, Torregrossa L, Pellegrini G, Molinaro E, et al. Elevated level of serum carbohydrate antigen 19.9 as predictor of mortality in patients with advanced medullary thyroid cancer. Eur J Endocrinol. 2015;173:297–304.
10. Milman S, Arnold JL, Price M, Negassa A, Surks MI, Fleischer N, et al. Medullary thyroid cancer that stains negative for CA 19-9 has decreased metastatic potential. Endocr Pract. 2015;21:590–4.
11. Ruffini E, Oliaro A, Novero D, Campisi P, Filosso PL. Neuroendocrine tumors of the thymus. Thorac Surg Clin. 2013;21:13–23.
12. Litvak A, Pietanza MC. Bronchial and thymic carcinoid tumors. Hematol Oncol Clin North Am. 2016;30:83–102.
13. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after 'carcinoid': epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26:3063–72.
14. Ahmad U, Yao X, Detterbeck F, Huang J, Antonicielli A, Filosso PL, et al. Thymic carcinoma outcomes and prognosis: results of an international analysis. J Thorac Cardiovasc Surg. 2015;149:95–100.
15. Georgy BA, Casola G, Hesselink JR. Thymic carcinoid tumors with bone metastases. A report of two cases. Clin Imaging. 1995;19:25–9.
16. Wu X, Qi Y, Yang F, Tan M, Lin J. Spinal metastasis resulting from atypical thymic carcinoid: a case report. World Neurosurg. 2018;111:373–6.
17. Kobashi Y, Shimizu H, Mouri K, Irei T, Oka M. Clinical usefulness of fluoro-2-deoxy-D-glucose PET in a case with multiple bone metastases of carcinoid tumor after ten years. Intern Med. 2009;48:1919–23.

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