Received: 14 June 2021 | Accepted: 27 August 2021

DOI: 10.1111/1759-7714.14153

CASE REPORT

WILEY

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 ^{18}F-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. Thoracoscopic thymothymectomy 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).

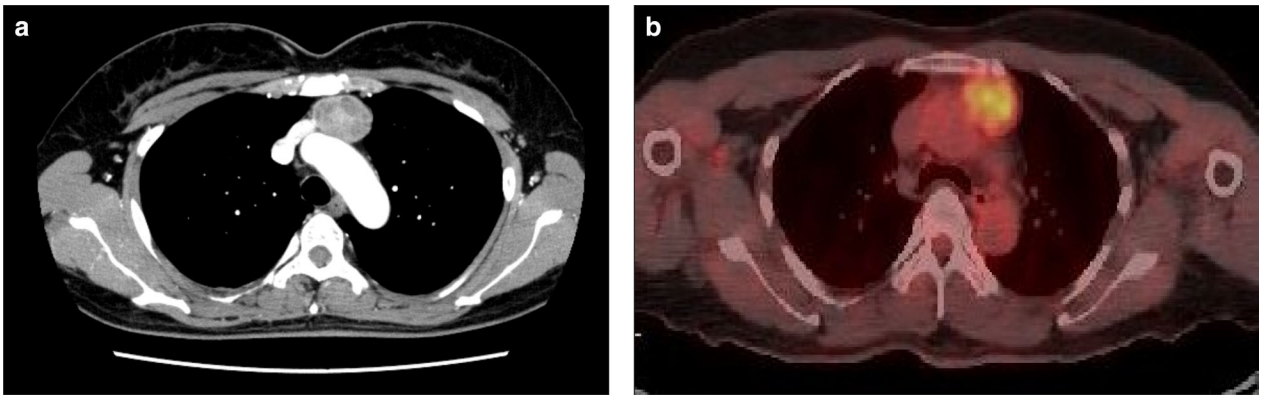

FIGURE 1 (a) Chest computed tomography showed an anterior mediastinal mass and (b) the mass was positive on positron emission tomography with ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (18-FDG-PET/CT)

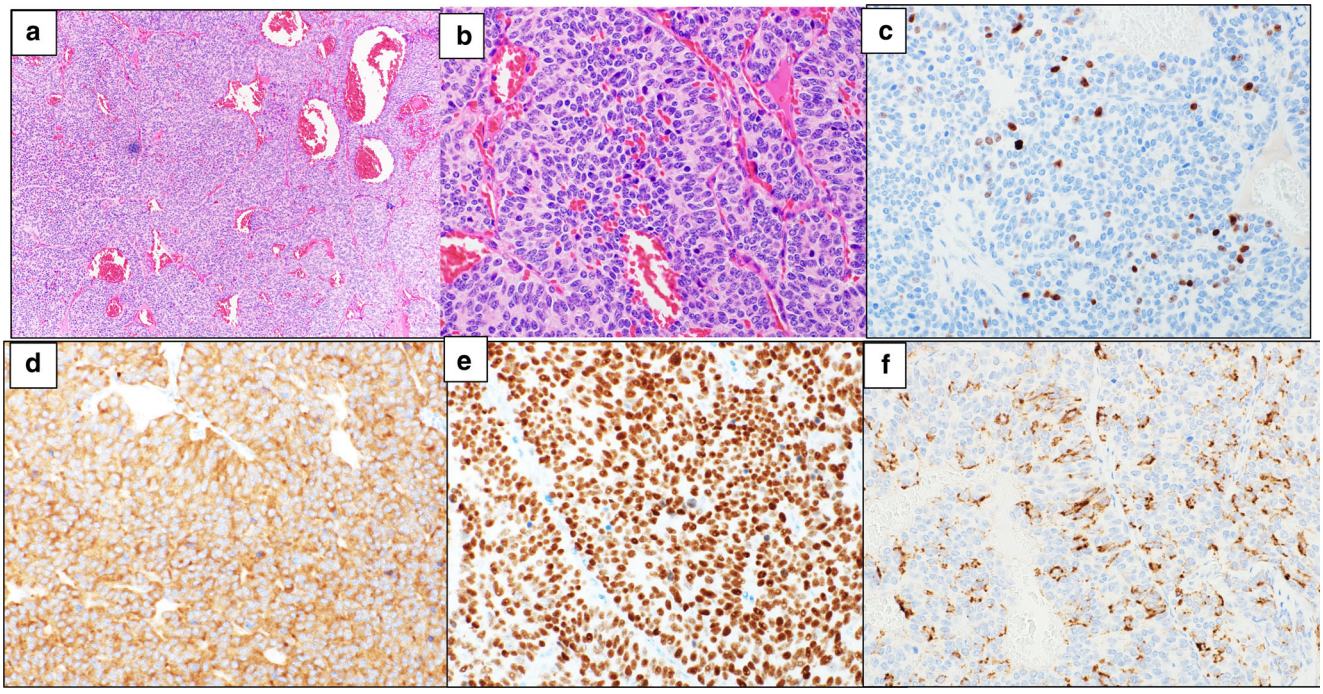

FIGURE 2 The pathological findings of the resected mass indicated irregularly shaped sheets and nests of tumor cells, and a diagnosis of neuroendocrine tumor was made (a, HE ×10; b, ×40). (c) The Ki-67 labeling index was 5.6%. (d) Immunohistochemical staining indicated that tumor cells were positive for synaptophysin, (e) insulinoma-associated protein 1, and (f) carbohydrate antigen 19-9

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

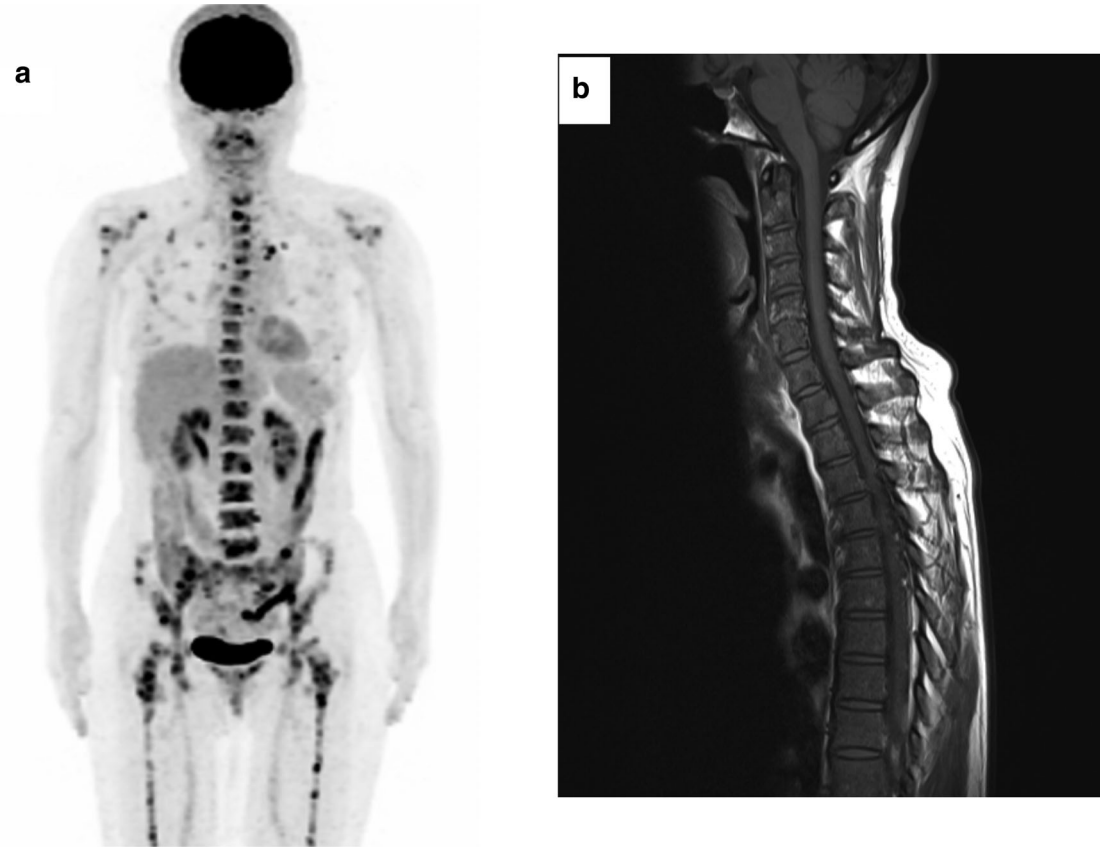

FIGURE 3 (a) Positron emission tomography with ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (18-FDG-PET/CT) showed diffuse and multiple FDG uptake in the thoracolumbar spine and iliac-sacrum, femur, and rib areas. (b) Magnetic resonance imaging on fat-suppressed contrast-enhanced T1-weighted images showed heterogeneous infiltration of the vertebra, suggesting multiple bone metastases

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.[1] 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.[6,7] Several studies of CA19-9 in pancreatic NET patients have been reported. Luo et al.[3] 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.[4] 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.[8–10] Therefore, elevated CA19-9 may be a predictor of poor prognosis and/or aggressive NET. Thymic NET is a rare clinical entity,[11,12] with poorer prognosis than foregut counterparts and with the potential for local and distant metastasis.[13,14] 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.[3,4]

Similar thymic NETs with multiple bone metastases have been reported,[15–17] with frequency ranging between 7% and 15% in NETs.[14] However, somatostatin analog and metaiodobenzylguanidine (octreotide) scintigraphy were used to evaluate bone metastasis and did not focus on thymic NETs. Kobashi et al.[17] 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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How to cite this article: Shimizu Y, Kanda S, Fukushima T, Kobayashi T, Kondo R, Koizumi T. Increased carbohydrate antigen 19-9 expression in a thymic neuroendocrine tumor. Thorac Cancer. 2021;12:2949–52. https://doi.org/10.1111/1759-7714.14153