Clinical Case Report

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Esophageal neuroendocrine carcinoma complicated with unexpected hyperprocalcitonin

Case report and literature review

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Abstract

Rationale: Neuroendocrine tumors (NETs) with hyperprocalcitonin are relatively rare with a low incidence rate.

Patient concerns: An afebrile 63-year-old male with persistent low back pain unexpectedly presented with an extreme hyperprocalcitonin. Radiological assessment revealed thickening of the esophageal wall with vertebral bone destruction and liver lesions. Endoscopy showed an irregular-shaped esophageal lesion which turned out to be poorly-differentiated NETs.

Diagnosis: Esophageal NETs with multiple metastases.

Interventions: The patient was treated with chemotherapies, and was evaluated by procalcitonin level and radiology within follow-up.

Outcome: The procalcitonin levels were altered in line with the therapeutic response and disease progression during the treatment course.

Lessons: Increased procalcitonin occurs in several malignancies with neuroendocrine components, such as NETs of the digestive system.

Abbreviations: CgA = chromogranin A, CT = computed tomography, NET = neuroendocrine tumor.

Keywords: hyperprocalcitonin, neuroendocrine tumors

1. Introduction

Neuroendocrine tumors (NETs) are neoplasms developing from the enterochromaffin cells located in neuroendocrine tissue throughout the body, namely in the intestine, pancreas, lung, and almost all other organs. However, esophageal NETs are very rare with a low incidence rate of approximately 1.3% of all gastrointestinal NETs.[1] A few cases concerning primary esophageal NETs have been previously reported, possibly because the neuroendocrine system is not well developed in the esophagus.[2] Heterogeneous presentations of NETs pose diagnostic challenges, which require physician to better understanding the functional or non-functional symptoms. One of the common presentations in NETs shares symptoms of carcinoid syndrome, associated with peptide hormone-producing features of NET cells. Hyperprocalcitonin is a common condition occurring in infectious diseases, where procalcitonin is produced ubiquitously in response to endotoxins or mediators are released in response to bacterial infections and strongly correlate with the extent and severity of bacterial infections.[3] Hyperprocalcitonin may also occur in several kinds of NETs, but there is no previous report of symptoms similar to carcinoid syndrome presenting with hyperprocalcitonin in esophageal NETs. Herein, we report a case of esophageal NET with unexpected hyperprocalcitonin, which was identified pathologically in a 63-year-old man.

2. Case report

A 63-year-old Chinese man presented with persistent low back pain that was unresponsive to physical therapy. The patient was afebrile. Unexpectedly, initial laboratory testing revealed extreme hyperprocalcitonin with values ranging from 36.2 to 42.5 ng/mL (reference value < 0.5 ng/mL), with a slightly elevated leukocyte count of 10.2×10^9/L, in the absence of severe systemic inflammatory response. He received antibiotics against possible infection, and the leucocyte count gradually became normal, whereas the procalcitonin level remained high. Computed tomography (CT) showed vertebral bone destruction which was understood to be the cause of his low back pain, multiple liver lesions, and thickening of the esophageal wall with enlarged lymph nodes (Fig. 1). However, the patient denied any significant epigastric discomfort. Further esophagogastroscopy revealed an

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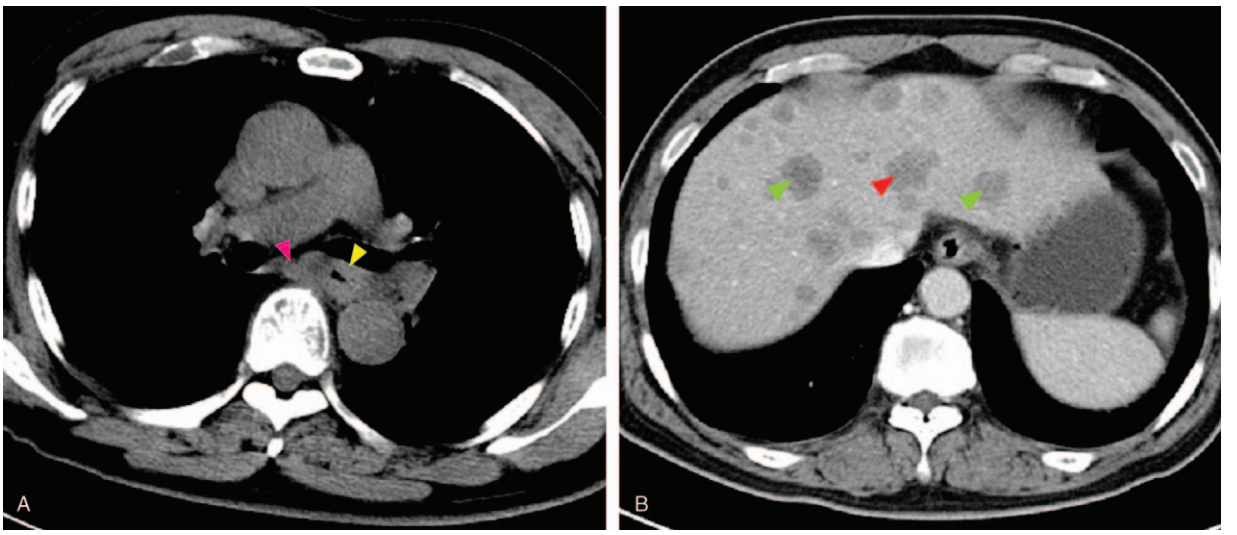

Figure 1. CT showed (a) thickening of the esophageal wall (yellow triangle) with enlarged lymph nodes (pink triangle), and (b) multiple liver metastases (red and green triangles). CT = Computed tomography.

irregular-shaped elevated lesion protruding toward the esophageal lumen with ulceration and covered by a white exudate at the middle thoracic esophagus (Fig. 2).

Biopsy from the ulcerative esophageal lesion suggested poorly differentiated NETs with a small-cell phenotype, featuring diffuse expression of synaptophysin (Syn), focal expression of chromogranin A (CgA), and weak positive staining of CD56 (Fig. 3). The patient then underwent chemotherapy with cisplatin and etoposide for esophageal NETs with liver and bone metastasis according to the multidisciplinary consult. The procalcitonin level dramatically dropped from 42.5 to 14.2 ng/mL right after the first cycle of chemotherapy, and eventually decreased to 6.5 ng/mL. CT reevaluation after completion of the second cycle suggested slight shrinking of the esophageal lesion but progression in some metastatic liver lesions (Fig. 4), as the procalcitonin level accordingly increased to 9.5 ng/mL. The chemotherapeutic regimen was then changed to cisplatin and irinotecan combined with radiation therapy owing to disease progression. The patient then developed obstructive jaundice, liver dysfunction, and subsequent hepatic encephalopathy after 2 cycles of cisplatin and irinotecan chemotherapy, and expired 2 months post chemotherapeutic regimen change. Informed patient consent was obtained from the patient for publication of this case report and accompanying images prior to treatment.

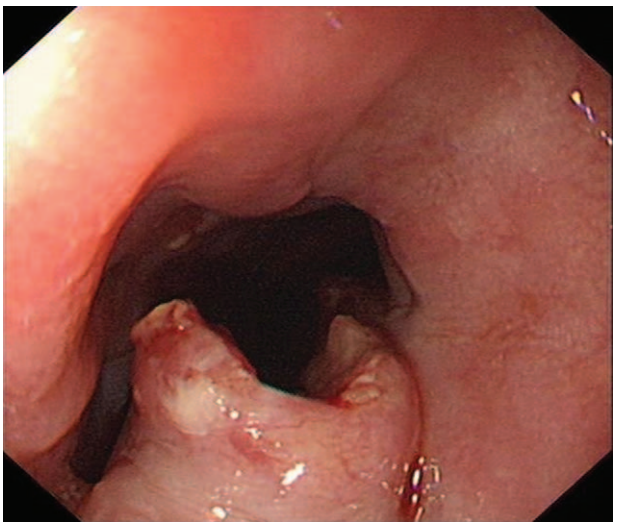

Figure 2. Esophagogastroscopy revealed an esophageal mass.

3. Discussion

The most interesting aspect of this case is the change in procalcitonin levels corresponding to therapeutic response and disease progression during the treatment course (Fig. 5). Procalcitonin, a precursor of calcitonin, which consists of 116 amino acids with a molecular weight of 13 kDa, is encoded by the *CALC-1* gene. Expression of *CALC-1* gene is elevated during bacterial infections and cause procalcitonin release from all parenchymal tissues. Therefore, serum procalcitonin level is typically evaluated in the diagnosis of early bacterial infections.[4]

Procalcitonin can also be produced by the neuroendocrine cells of the lung and the alimentary tract, where NETs might develop, as for instance in our case, an esophageal NET.[5] Elevated procalcitonin levels might be found in many kinds of neoplasms such as thyroid medullar carcinoma and small-cell lung carcinoma, exhibiting paraneoplastic production. To further investigate the association between NETs and procalcitonin, we conducted a literature review on this specific subject. We searched the MEDLINE and EMBASE databases using the keywords "(NETs OR neuroendocrine carcinomas OR neuroendocrine neoplasms) AND procalcitonin". The final date of data collection was in April 2017. A total of 46 results were initially obtained, and the articles irrelevant to NETs were excluded. Finally, 19 eligible articles were included that consisted of 9 clinical series studies, 4 case reports, and 3 review articles (the clinical series studies and case reports are respectively summarized in Table 1 and Table 2).

Based on approaches from current studies, along with our data, we suggested that serum procalcitonin levels be used as a diagnostic marker in several malignancies with neuroendocrine components. The most common cancer with hyperprocalcitonin is medullary thyroid carcinoma, a neuroendocrine tumor arising from the parafollicular cells.[6] In patients with active medullary

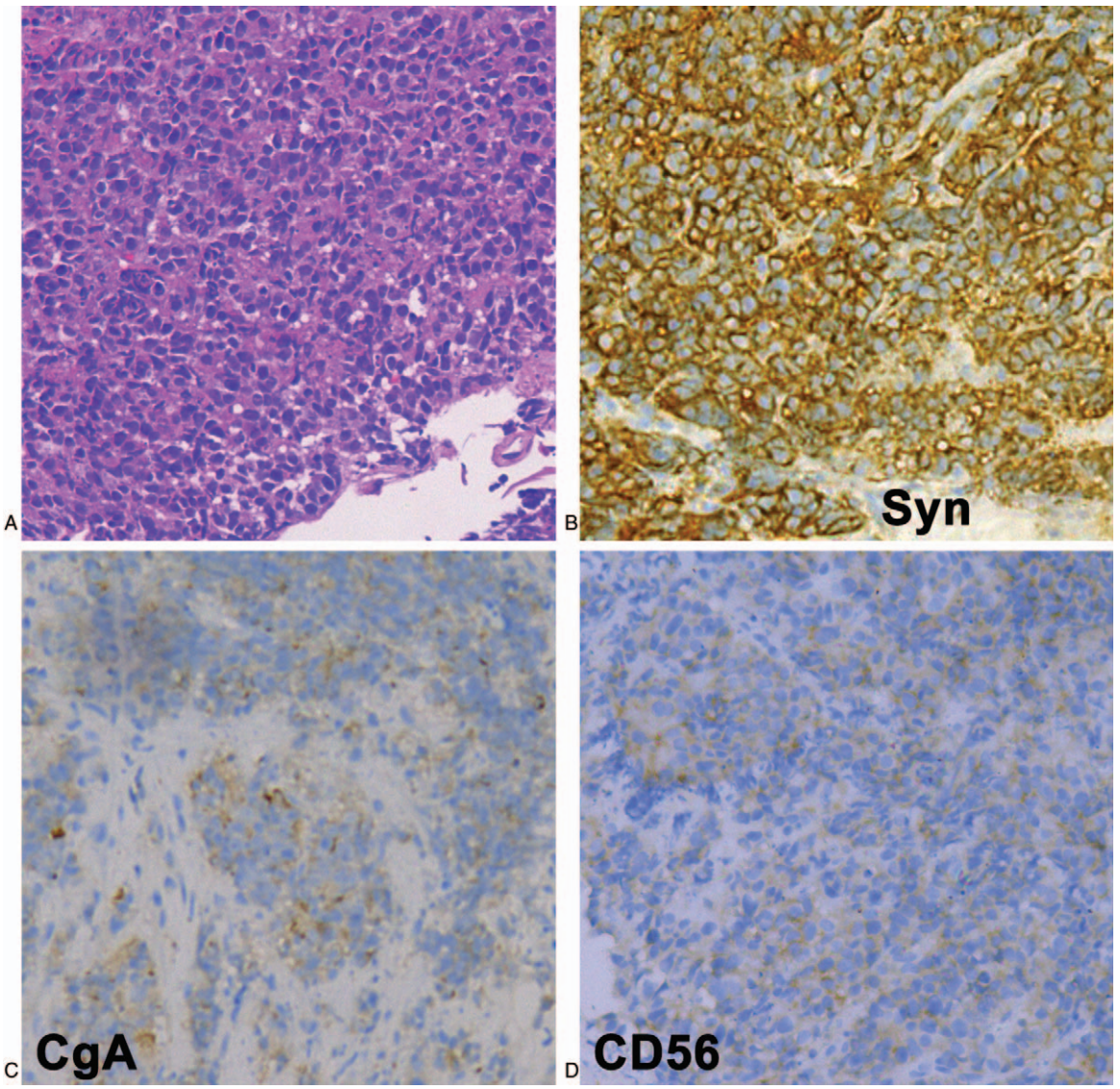

Figure 3. Biopsy pathology suggested poorly differentiated NETs with (a) a small-cell phenotype, featuring (b) diffuse expression of Syn, (c) focal expression of CgA, and (d) weak positive staining of CD56. CgA = chromogranin A, NET = neuroendocrine tumor, Syn = synaptophysin.

thyroid carcinoma, the procalcitonin level was usually elevated and decreased after surgery or other treatment approaches.[7] Pomorski et al showed that the serum procalcitonin was higher in active medullary thyroid carcinoma with a mean level of 3.5 ng/mL, while the normal range was less than 0.5 ng/mL. Interestingly, an operative medullary thyroid carcinoma patient in their study received radical resection as the serum procalcitonin level decreased dramatically from 10.16 ng/mL to 0.32 ng/mL at 3 weeks postoperatively. Meanwhile, the procalcitonin could also indicate disease activity in medullary thyroid carcinoma, as procalcitonin levels in the metastatic or recurrent stage (13.1 ng/mL) was significantly higher than the stable stage (0.6 ng/mL) or the cured patients (< 0.1 ng/mL).[8] Another common cancer presented with hyperprocalcitonin is lung cancer, including small-cell carcinoma and large-cell carcinomas with a neuroendocrine component.[9] Patout et al reported that the median procalcitonin levels varied significantly among different histological types, and an elevated procalcitonin level more than 0.15 ng/mL was associated with the histological types with a neuroendocrine component.[5] Specifically, small-cell lung carcinoma tends to have a higher procalcitonin level (0.33 ng/mL) than pulmonary adenocarcinomas (0.07 ng/mL). However, the sensitivity and specificity for detecting the neuroendocrine component in lung carcinoma using procalcitonin were unsatisfying.[5]

Digestive NETs are relatively rare compared to medullary thyroid carcinoma or small-cell lung carcinoma with neuroendocrine components. Hyperprocalcitonin, as a symptom presented similar to carcinoid syndrome, is therefore extremely rarely reported in NETs of the digestive system. Abnormal procalcitonin secretion was only reported in 1 clinical series study and 1 case report. A Japanese group reported a grade 3 pancreatic NET case (World Health Organization classification), featured with neuron-specific enolase and procalcitonin elevation,[10] whose serum procalcitonin level also reflected the therapeutic effect. Recently, a Chinese group analyzed 63 patients (40.6%) with NETs primarily occurring in the digestive system, including 31 with digestive tract tumors, and showed that elevated procalcitonin level was correlated with higher neuroendocrine grade and distant metastasis.[11]

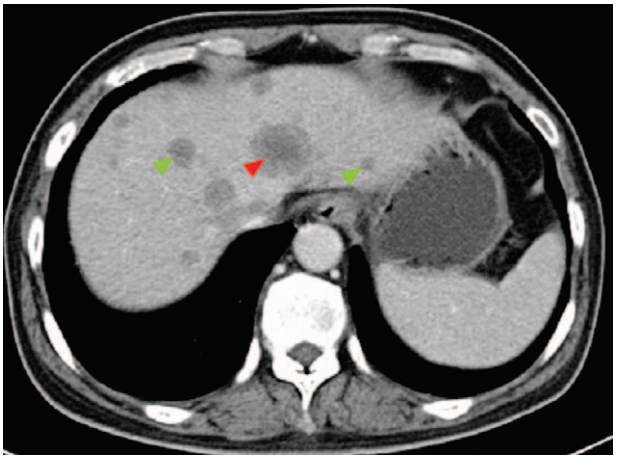

Figure 4. CT re-evaluation after 2 cycles of chemotherapy showed slight shrinking of the esophageal lesion and mostly metastatic liver lesions (green triangles), but progression in some metastatic liver lesions (red triangle), compared to the pre-chemotherapy CT results in Figure 1. CT = Computed tomography.

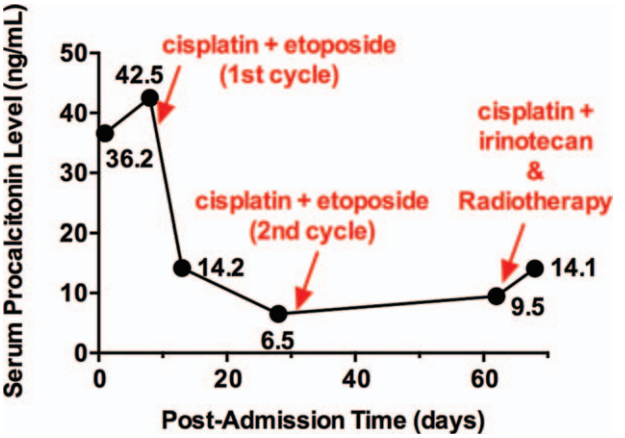

Figure 5. Procalcitonin level curve during the treatment course.

Table 1

Summarized series studies with increased procalcitonin in non-infectious scenarios.

First Author	Year	Country	Tumors Studied (Sample Size, N)	Main Findings	Ref.
Matzaraki	2007	Greece	Non-metastatic solid tumor (21) Liver metastases (11) Generalized metastases (11)	* Procalcitonin significantly increased with advanced metastatic stage in solid tumors.	(6)
Algeciras-Schimnich	2009	USA	Active MTC (91) Cured MTC (42) Non-MTC NET (225) Persistent FTC (55) Cured FTC (120)	* Procalcitonin was elevated in 9.78% of non-MTC NET (22/225), 91.2% of active MTC (83/91), and 5.45% of FTC (3/55), but not in cured MTC and FTC. * Diagnostic sensitivity and specificity of procalcitonin for MTC were 91% and 96%, respectively.	(7)
Walter	2010	Switzerland	MTC (69)	* Diagnostic sensitivity and specificity of procalcitonin for MTC were 84.1% and 84.0%, respectively. * Procalcitonin:calcitonin ratio was associated with MTC progression	(8)
Kratzsch	2011	Germany	MTC (13)	* Procalcitonin helps the diagnosis of medullary thyroid cancer for patients with questionable increases in calcitonin.	(9)
Giovanella	2013	Switzerland	MTC (14)	* Procalcitonin was elevated in MTC patients with increased calcitonin level (diagnostic sensitivity and specificity: 100%)	(10)
Machens	2014	Germany	MTC (112)	* Procalcitonin elevation was associated with primary tumor size and lymph node metastasis.	(11)
Patout	2014	France	LAC (67) SCLC (51) SCC (21) LC (6) Sarcoma (2)	* Neuroendocrine component was an independent risk factor for increased procalcitonin [odds ratio 5.1 (95% CI: 1.3–20.2), $p = 0.02$]. * Diagnostic sensitivity and specificity of procalcitonin for liver metastases were 66% and 69.4%, respectively. * Increased procalcitonin was associated with poor prognosis ($p < 0.001$).	(5)
Avrillon	2015	France	Lung cancer (89)	* Elevated procalcitonin was found in 41.6% of patients (37/89). * Neuroendocrine component was associated with positive procalcitonin [odds ratio 7.24 (95% CI: 1.91–27.51), $p = 0.004$]. * Baseline procalcitonin elevation was found in 43% of NSCLC with a neuroendocrine component.	(12)
Chen	2017	China	Digestive NET (155)	* Increased procalcitonin was found in 40.6% of digestive NETs (63/155). * Procalcitonin elevation was associated with higher NET grade. * Change of procalcitonin level was associated with the therapeutic response. * Intratumoral procalcitonin expression was positive in 24% of tumor specimens (23/96).	(13)

FTC = follicular thyroid carcinoma, LAC = lung adenocarcinoma, LC = large cell lung cancer, MTC = medullary thyroid carcinoma, NET = neuroendocrine tumor, NSCLC = non-small cell lung cancer, SCLC = small-cell lung cancer, SqCLC = squamous cell lung cancer.

Table 2

Summarized case reports with increased procalcitonin in non-infectious scenarios.

First Author	Year	Country	Tumors Studied	Metastasis	Pretreatment Procalcitonin Level (ng/mL)	Treatment	Notes	Ref.
Bugalho	2014	Portugal	MTC	Lymph node	10.3	Surgery + Sunitinib		(14)
Brutsaert	2015	USA	MTC	No	0.21	Surgery		(15)
Trimboli	2016	Switzerland	MTC	No	1.1	Surgery	Postoperative procalcitonin level decreased to normal	(16)
Hagiya	2017	Japan	Pancreatic NET	Liver metastases	99.52	Chemotherapy (irinotecan + cisplatin)	Positive procalcitonin staining in specimen	(17)

MTC = medullary thyroid carcinoma, NET = neuroendocrine tumor.

In our case, the serum procalcitonin level changed corresponding to the therapeutic effect on metastasis and primary tumor, consistent with conclusions from previous case reports.[11] Notably, our case is unique, because the serum procalcitonin level was critically high (>100 ng/mL) and the treatment outcome was positive (partial response). The abnormal hyperprocalcitonin level in our case was possibly associated with several factors. First, the neuroendocrine nature of the disease, namely poorly differentiated carcinoma, contributed to the abnormal elevation of the procalcitonin base level. Second, the patient initially presented with multiple metastasis, mostly with more severe complications including critically high procalcitonin. Finally, the procalcitonin level accompanying the esophageal NETs was sensitive to effective treatment and disease progression, resulting in high-margin elevation corresponding to disease status.

This case report and literature review also have some limitations. First, the biopsied samples were not further tested for mutation detection and genome sequencing, which might provide a more personalized management plan, such as treatment with targeted agent or immune checkpoint inhibitor, to achieve better survival. Second, current methods to determine the procalcitonin expression in tissue samples still lack efficacy, which constrains our investigation on association between the intratumoral procalcitonin expression and the serum procalcitonin level. Third, the absence of consensus or guidelines on management of NET with abnormal marker elevation led to unclear definition of marker elevation, which resulted in various criteria for diagnosis of procalcitonin elevation in different kinds of literature.

In summary, we presented a rare case of esophageal neuroendocrine carcinoma complicated with unexpected hyperprocalcitonin. Procalcitonin elevation is sometimes associated with cancer status and disease progression in NETs. Unexpected hyperprocalcitonin should be carefully investigated for possible NETs in patients with no significant sign of severe infection.

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Author contributions

QH, XZ, BH, SS, and RQ treated the patients and collected all the data of the case; TL supervised the treatment; QH, PJ, and WW reviewed literatures and wrote the manuscript; RQ and TL revised the manuscript; and TL approved the final version.

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