NOTE

Functional Giant Parathyroid Cyst with High Concentration of CA19-9 in Cystic Fluid

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Abstract. A 63-year-old man was admitted to our hospital for the evaluation of hypercalcemia and anterior neck mass. Laboratory findings revealed hypercalcemia, hypophosphatemia, and hypercalciuria, as well as elevated serum levels of parathyroid hormone (PTH) and alkaline phosphatase. Computerized tomography and magnetic resonance images showed that the mass contained a cystic area. Parathyroid scintigraphy using either ^{99m}Tc -sestamibi alone or ^{201}Tl -chloride in conjunction with ^{99m}Tc -pertechnetate for thyroid image subtraction showed uptake of the radioactivity into the cyst wall, suggesting that the mass originated from the parathyroid. Fine needle aspiration biopsy revealed that the cyst fluid was serous and bloody with extremely high concentrations of both PTH and CA19-9. The patient was diagnosed as primary hyperparathyroidism caused by parathyroid cyst and cervical exploration was performed. The cyst was dissected away along with the right lobe of the thyroid gland. After tumor removal, serum calcium and PTH levels were normalized. Histological study showed that the tumor possessed malignant potential with capsular invasion as well as moderate cellular atypia with trabecular pattern in arrangement. Parathyroid cells in the wall of the cystic tumor were immunostained positively for CA19-9, suggesting that CA19-9 in the cyst fluid was produced from the cells.

Key words: Parathyroid cyst, Primary hyperparathyroidism, CA19-9, Parathyroid carcinoma, Scintigraphy
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PARATHYROID cysts are relatively rare compared to thyroid cysts. In general, parathyroid cysts are divided into two groups, functioning and non-functioning ones. Functioning cysts with hypercalcemia contain high concentration of parathyroid hormone (PTH) in cyst fluid. Non-functioning cysts also have high concentration of parathyroid hormone but do not cause hypercalcemia. Moreover, parathyroid carcinomas occur in less than 1% of primary hyperparathyroidism [1] and are difficult to diagnosed before

surgical operation. Several case reports suggested the usefulness of immunohistochemical evaluation of CA19-9 in thyroid papillary carcinoma [2, 3], but there have been no reports about CA19-9 in parathyroid cysts. We here present a case of functional giant parathyroid cyst containing high concentration of CA19-9 in cyst fluid.

Case reports

A 63-year-old man was admitted to our hospital for hypercalcemia as well as a slowly growing mass in his anterior neck, which had been noticed 1 year earlier. He did not have any symptoms related to hypercalcemia. On physical examination, a 7.0×6.6 cm mass was palpable in the right anterior neck. It was elastic and adherent to the skin. Laboratory findings showed

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hypercalcemia, hypophosphatemia, and hypercalciuria, as well as elevated serum levels of PTH and non-specific alkaline phosphatase (ALP). Thyroid function was normal (Table 1). Computerized tomography (CT) showed that the cystic mass having a septal structure on the inside was located in the right lobe of the thyroid (Fig. 1). High intensity images of its contents on both T1 and T2-weighted magnetic resonance images (MRI) suggested that the cystic area was composed of bloody solution (Fig. 2). Parathyroid scintigraphy using either ^{99m}Tc -sestamibi alone or ^{201}Tl -chloride in conjunction with ^{99m}Tc -pertechnetate for thyroid image subtraction showed intense accumulation of radioactivity in the wall of the cystic mass (Fig. 3). Fine needle aspiration biopsy of the cystic fluid was performed under ultrasonography. The fluid appeared bloody and serous, and contained extremely high concentrations of intact-PTH, midregion-PTH, and CA19-9, compared to their serum levels (200,000 pg/ml vs. 350 pg/ml, 2,800,000 pg/ml vs. over 3200 pg/ml, and 2766 U/ml vs. 6 U/ml, respectively) (Table 2). Cytological evaluation of the fluid was negative for malignancy. The patient was diagnosed as primary hyperparathyroidism with parathyroid cyst, and cervical exploration was performed. The tumor was dissected away with right lobe of thyroid gland from the surrounding tissue. The cyst was filled with about 80 ml of bloody fluid. On histological study, parenchymal cells showed moderate cellular atypia with trabecular and palisading patterns in arrangement. The finding of capsular invasion suggest-

ed that the tumor had malignant potential (Fig. 4). However, the definitive diagnosis of parathyroid carcinoma was difficult, because neither vascular invasion nor metastasis to local lymphnodes were observed. Immunohistochemical staining was performed using formalin-fixed and paraffin-embedded sections. Sections were deparaffinized in xylene and dehydrated through an ethanol series [4]. Endogenous peroxidase was then inactivated with 0.3% H_2O_2 in methanol for 20 min at room temperature. After blocking with 1.5% nonfat dry milk in PBS for 10 min, sections were incubated with mouse anti-human CA19-9 antibody (Japan Tanner Technological Laboratories Co., Osaka, Japan) overnight at 4°C. After washing with PBS, samples were incubated with a biotinylated-linking antibody and peroxidase-labeled streptavidin using an LSAB2 kit (Dako Corp., Carpinteria, CA, USA) for 30 min. Final development was carried out with 3,3-diaminobenzidine (DAB) containing 0.1% H_2O_2 in PBS for 10 min. Immunostaining examination showed that parathyroid cells in the wall of the cystic tumor were positive for CA19-9 (Fig. 5), suggesting that CA19-9 in the cyst fluid was secreted from tumor cells. After removal of the tumor, serum levels of calcium and PTH were normalized.

Table 1. Laboratory findings of blood examination

FT_3 (3.5–6.3 pmol/l)	4.6
FT_4 (12.6–22.0 pmol/l)	18.1
TSH (0.362–4.044 mU/l)	0.793
Ca (2.10–2.48 mmol/l)	3.2
P (0.77–1.45 mmol/l)	0.84
Alb (41–50 g/l)	36
ALP (100–303 IU/l)	680
U-Ca/day (mmol)	12.0
CCa/CCr	0.023
%TRP	81.2
midregion-PTH (160–520 pg/ml)	>3200
intact-PTH (10–65 pg/ml)	350
CA19-9 (<37 U/ml)	6

Abbreviation: CCa/CCr: calcium clearance/creatinine clearance

Fig. 1. CT image showing that mass is located in the right lobe of the thyroid, pushing surrounding organs aside. A cystic area can be observed inside the mass.

Fig. 2. High intensity imaging of the contents in the cystic space on both T1- (left) and T2- (right) weighted MRI suggested that the cystic area was full of hemosiderin-containing fluid and sanguineous.

Fig. 3. Parathyroid scintigraphy using either ^{99m}Tc -sestamibi alone (a) or ^{201}Tl -chloride in conjunction with ^{99m}Tc -pertechnetate for thyroid image subtraction (b) showed intense ringed accumulation of radioactivities into the wall of the cystic mass.

Table 2. Laboratory findings in cyst fluid

FT ₃ (pmol/l)	5.1
FT ₄ (pmol/l)	15.3
midregion-PTH (pg/ml)	2800000
intact-PTH (pg/ml)	200000
CA19-9 (U/ml)	2766

Discussion

Parathyroid cysts are relatively rare and their exact incidence varies from 0.08% to 3.4% [5]. In general, parathyroid cysts are divided into two groups, func-

tioning and non-functioning, but Mallette [6] suggested that they were classified into three categories based on the presumptive mechanism of cyst formation: ontogenous parathyroid cyst (congenital), coalescence parathyroid cyst (coalescence of microcysts) and parathyroid pseudocyst (infarction within a parathyroid adenoma). Our case was considered to be the latter type, judging from image analysis and histological findings. It has been reported that fine needle aspiration is useful to distinguish parathyroid cysts from thyroid cysts, because parathyroid cysts have high concentration of PTH in cyst fluid [7].

Few previous reports have demonstrated the scintigraphy of the cystic parathyroid tumor. Although the

Fig. 4. Histopathological features of parathyroid cyst:
 (a) trabecular pattern in the arrangement of parenchymal cells
 (b) cellular atypia
 (c) capsular invasion

Fig. 5. Immunohistochemical analysis for CA19-9: Parathyroid cells in the wall of the cystic tumor were positive for CA19-9.

mass was clearly identified by CT and MRI in the present case, parathyroid scintigraphy seemed to give some additional useful information as to the nature of the mass. In particular, scintigraphy showed intense ring-shaped accumulation of radioactivity in the wall of the cystic mass in the present case, suggesting that the cyst wall consisted in large part of parathyroid

tissue, and that the cystic tumor was presumably a pseudocyst caused by infarction within the tumor.

The diagnosis of parathyroid carcinoma is usually made when the following criteria are fulfilled histologically: a trabecular or palisading pattern in the arrangement of parenchymal cells, mitotic figures in parenchymal cells, thick fibrous bands coursing through the tumor, and invasion of the capsule or blood vessels by tumor cells [6]. The potentially malignant nature of the present tumor was suggested by the finding of capsular invasion as well as moderate cellular atypia with trabecular pattern in arrangement. However, we could not diagnose the tumor as a definite parathyroid carcinoma because of the lack of certain criteria. In general, it is difficult to diagnose parathyroid carcinoma preoperatively without its apparent metastasis or invasion to the surrounding tissue. Abnormal parathyroid tissue has been reported to synthesize or secrete various biologically active substances, such as PTH-related protein [8], calcitonin [9], calcitonin gene-related peptide [10], gastrin [11], somatostatin [12], hCG [13], and pancreatic polypeptide [14]. However, none of these substances was useful for diagnosing parathyroid carcinoma.

In the present case, the concentration of CA19-9 in cystic fluid was extremely high and the parathyroid cells in the wall of cystic tumor were positively immunostained for CA19-9. Various tumors including benign and malignant ones produce CA19-9. CA19-9 was reported to be produced from some thyroid papillary carcinoma [2, 3]. Moreover, follicular lining cells of anterior pituitary display CA19-9 at their luminal surface [15]. Expression of CA19-9 in adenohypophysis might be related to its origin from an anlagen, the stomodeum shared with the parotid gland. Taking this into account the endocrine character in the present case may be related to the production of CA19-9. However, the occurrence of CA19-9 production from normal parathyroid cells or parathyroid adenoma is still unknown, and further study is needed to clarify this issue. Alternatively, the cyst-forming character might be the cause of CA19-9 production. Hammel *et al.*

[16] reported that preoperative cyst fluid analysis is useful for the differential diagnosis of cystic lesions of the pancreas. In the present case, high CA19-9 level in cyst fluid was highly indicative of mucinous tumor. Therefore, some cystic types of parathyroid tumor might be related to the release of CA19-9 into cystic fluid. But, whether CA19-9 is associated with malignant parathyroid tumor cannot be known from the present case.

In the present case, the serum level of CA19-9 was within the normal range, although the concentration of CA19-9 in the cystic fluid was much higher. The reason for this difference is unclear. The tumor size or the amount of cells producing CA19-9 might not have been great enough to elevate the serum level of CA19-9. Alternatively, there was the possibility that CA19-9 was released mainly into the cystic fluid, and not the vessels.

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