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Case Report

Recurrent hyperparathyroidism due to parathyroid and pulmonary tumors showing features of parathyroid adenoma [☆]

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ABSTRACT

We report on a case of recurrent primary hyperparathyroidism possibly caused by parathyroid adenocarcinoma metastasizing to the lung. A 46-year-old woman with a history of parathyroid adenoma, which was extirpated 8 years ago, presented with symptoms of primary hyperparathyroidism, and was found to have a parathyroid and a lung nodule in radiographic assessments. Resections of the tumors in the parathyroid gland as well as the lung were required to improve her condition, and in pathology, both tumors demonstrated benign features consistent with adenoma. However, from the perspective of the clinical course and location of the tumors, we deduced that the tumors were malignant despite being identified as benign by conventional pathological examination. The integration of information based on clinical status and imaging studies is essential to evaluate the malignant potential of tumors if a patient with hyperparathyroidism has tumors located both inside and outside of the parathyroid gland.

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Introduction

Several conditions cause primary hyperparathyroidism, but 85% of cases are caused by a single parathyroid adenoma

[1]. An ectopic parathyroid adenoma is occasionally found in the mediastinum, which is responsible for the state of hyperparathyroidism [2]. However, none of parathyroid adenomas metastasizing to other organs has been reported. Herein, we present a case of recurrent hyperparathyroidism with parathyroid and lung tumors that were clinically considered

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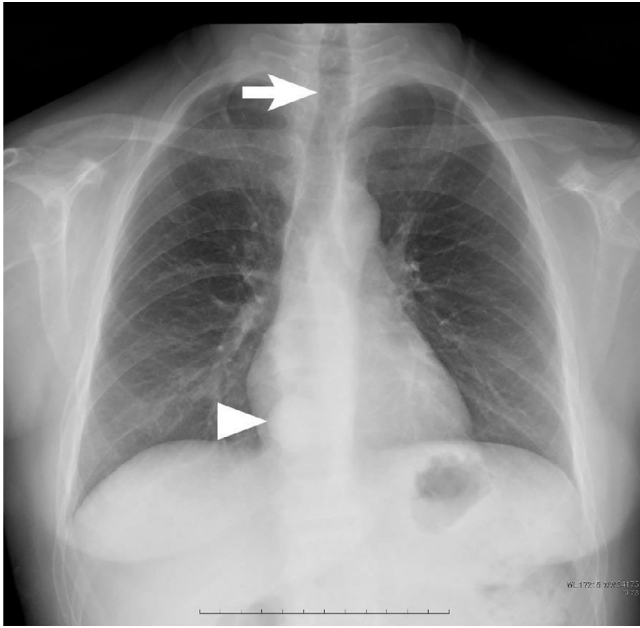


Fig. 1 – A chest radiograph. Tracheal deviation (arrow) and a nodule in the right lower lung field (arrowhead) are identified.

malignant even with pathologically consistent parathyroid adenoma.

Case report

A 46-year-old woman presented at our hospital with symptoms of dry mouth, fatigue, and arthralgia. Her family history was not significant. She had had the same symptoms in 8 years before presentation when a parathyroid adenoma at the inferior region of the right thyroid gland was discovered, which was subsequently resected. Her symptoms had subsided since then. She underwent annual checkups, and a nodule in the right lower lung field was found in a chest radiograph 1 year before presentation, but she was without symptoms at that time. She was recommended for continued follow-ups. One month prior to presentation, she started to experience dry mouth, fatigue, and arthralgia and sought medical help because of worsening symptoms. Her vitals were within normal limits, and her level of consciousness was normal. No masses were found during physical examinations of her neck. Blood levels of potassium, calcium, and parathyroid hormone were 2.3 mEq/L, 15.2 mg/dL, and 2300 pg/mL, respectively. She was diagnosed with primary hyperparathyroidism based on the clinical and biochemical examinations.

Imaging studies were conducted to identify the lesion. A chest radiograph (Fig. 1) showed a lung nodule 25 mm in diameter in the right lower lung field, which was the same size as seen during the annual checkup. The trachea was deviated to the left at the level of the first thoracic vertebrae. Computer-assisted tomography scans (Aquilion, Canon Medical, Tochigi, Japan) demonstrated a nodule adjacent to the right lobe of the thyroid gland (Fig. 2) and another nodule in the right lower lobe of the lung (Fig. 3). Both lesions were round and well-demarcated. ^{99m}Tc -methoxy isobutyl isonitrile (MIBI) scinti-



Fig. 2 – A CT scan in the neck. A nodule adjacent to the right lobe of the thyroid gland is seen (arrow).



Fig. 3 – A CT scan in the chest. A nodule in the lower lobe of the right lung is shown (arrow).

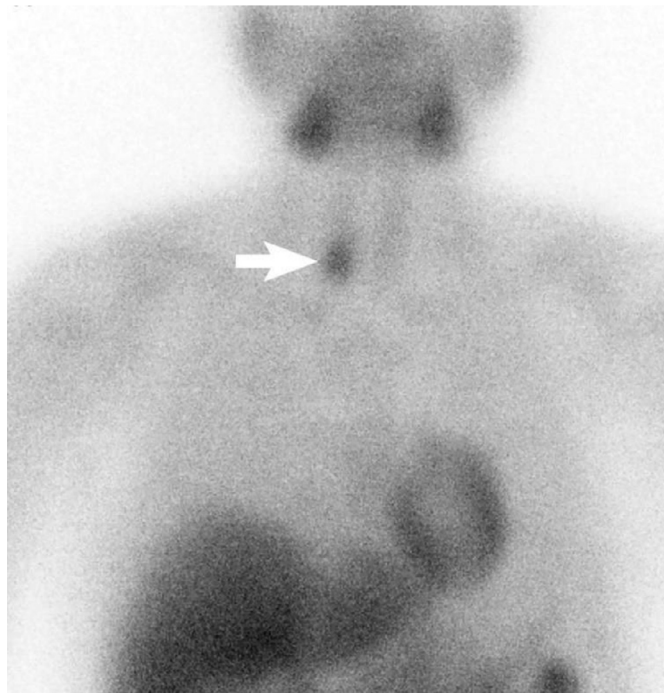


Fig. 4 – ^{99m}Tc -MIBI scintigraphy. Radioisotope accumulation is seen at inferior region of the right thyroid gland.

graphs (Figs. 4 and 5) showed radioisotope accumulation in both lesions. At this point, the parathyroid nodule in the neck was deemed to be responsible for her symptoms, and this nodule was surgically removed. Pathologically, it showed a normal rim of the parathyroid gland and lacked an irregularly shaped

nucleus (Fig 6). It had a Ki-67 labeling index of 3%-4%. The resected nodule was diagnosed as an adenoma. Despite the surgical procedure, her symptoms did not subside. The lung nodule was also resected and stained with parathyroid hormone dye. The pathological features were identical to those of the

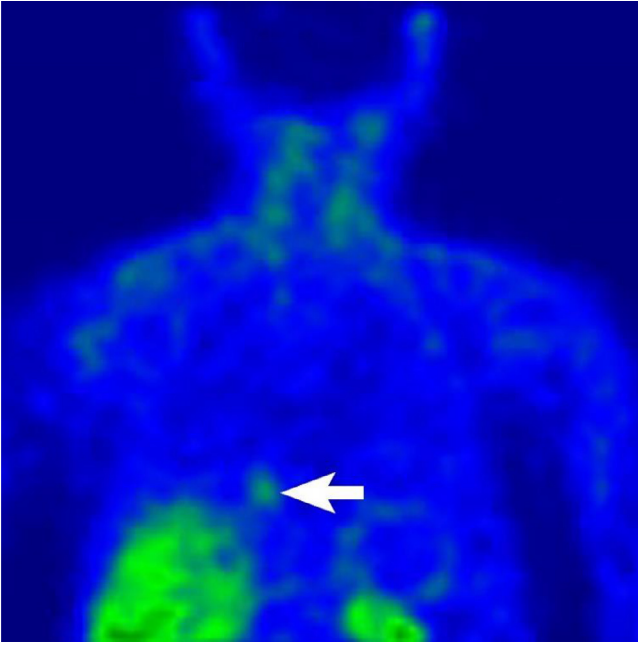


Fig. 5 – A reconstructed coronal image of single photon emission computed tomography. Radioisotope accumulation in the chest is seen (arrow).

parathyroid tumor and lacked any findings that would suggest malignancy (Fig. 7). Furthermore, a sample of the parathyroid gland taken 8 years ago was retrospectively reviewed (Fig. 8); however, the histopathological findings were similar to those of the parathyroid and lung and were consistent with adenoma. Her symptoms subsided following surgery.

Discussion

Our case showed recurrent hyperparathyroidism with parathyroid and pulmonary lesions with features of adenomas in conventional pathological examinations. The patient had previously presented with a parathyroid nodule that was resected 8 years ago and was pathologically determined to be an adenoma. The pathological diagnosis of adenoma at that time remained the same, even retrospectively. The findings from the parathyroid gland and lung at this time were also similar to those previous findings. We initially felt that the nodule in the lung was a functioning ectopic adenoma. However, an ectopic adenoma is usually found in the paraesophageal region or the mediastinum [2], and to the best of our knowledge, there are no reports showing ectopic parathyroid glands located in the lung tissue. Therefore, we deduced that the lung nodule was a functioning tumor that had possibly metastasized from the parathyroid tumor.

It is difficult to make a precise pathological distinction between benign and malignant parathyroid tumors by their appearance under microscopic views alone. Ki-67 is widely used to characterize parathyroid nodules in pathology laboratories, where a labeling index $> 5\%$ indicates an increased risk for

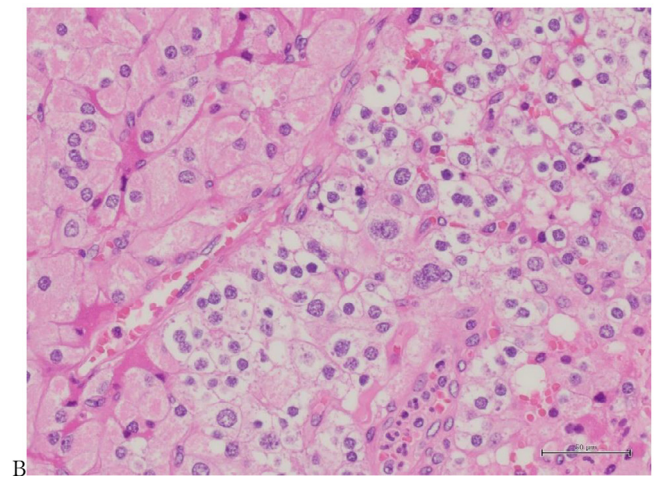
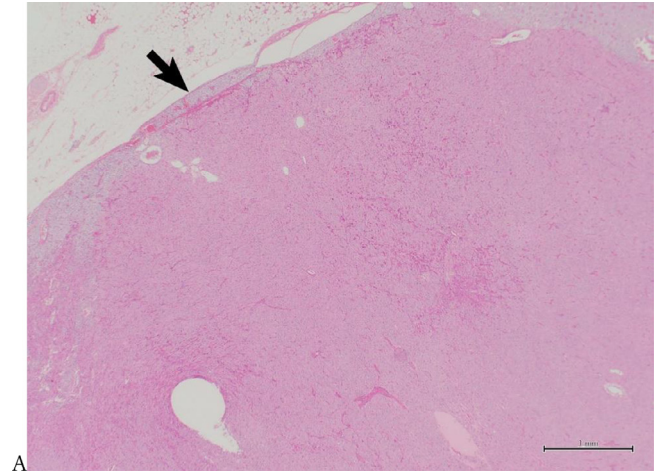


Fig. 6 – Parathyroid gland tissue. (A) Hematoxylin and Eosin (H&E) Stain, magnification $\times 20$. Normal rim of parathyroid gland is shown (arrow). (B) H&E Stain, magnification $\times 400$. No significant nuclear atypia is identified.

malignancy [3]. In addition, nuclei pleomorphisms viewed in tissues stained with hematoxylin and eosin are frequently noted in adenocarcinoma [3]. In this case, the labeling index was 3%–4%, and no significant nuclear atypia and surrounding tissue invasion were identified, likely indicating benignity. However, the Ki-67 labeling index has some diagnostic limitations, and a value of $<5\%$ does not rule out the possibility of malignancy. Inactivating mutations of CDC73 (HRPT2), a tumor suppressor gene, are the most common genetic changes seen in parathyroid carcinoma, in contrast to their rarity in sporadically presenting benign parathyroid adenomas [4]. Immunohistochemical expression of the protein product of CDC73 is lost in a majority of sporadic parathyroid carcinomas, unlike in sporadic adenomas. CCND1 gene amplification is also frequently observed in parathyroid carcinomas [4]. These investigations are not widely performed in clinical practice and could not be done in this study. Therefore, a clinical perspective is essential to interpret potential malignancy.

In terms of the imaging studies, ^{99m}Tc -MIBI showed radioisotope accumulation in the neck and lung nodules. How-

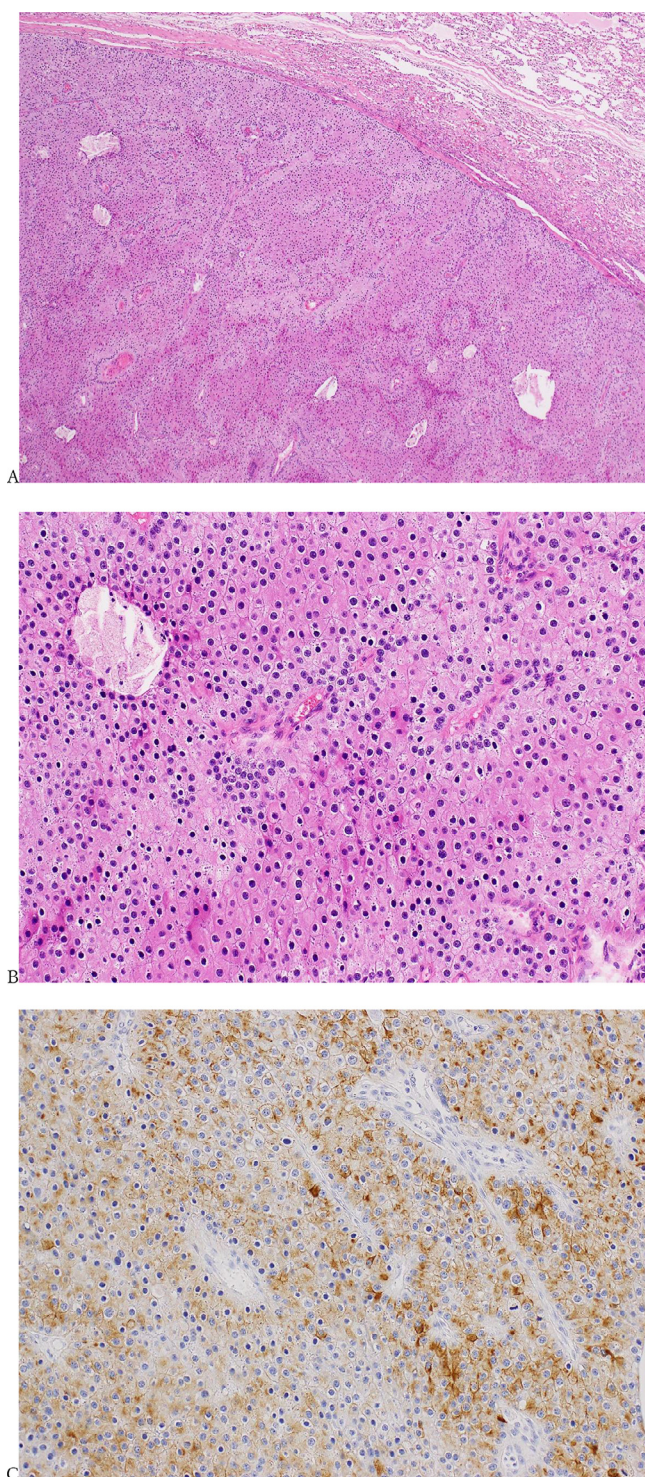


Fig. 7 – Lung tissue. (A) H&E Stain, magnification $\times 20$. Clear margin of the tumor and lung tissue is shown. (B) H&E Stain, magnification $\times 400$. No nuclear atypia is identified. (C) The tumor cells are stained with immunochemical stain for parathyroid hormone, which indicates the origin of the tissue is parathyroid gland.

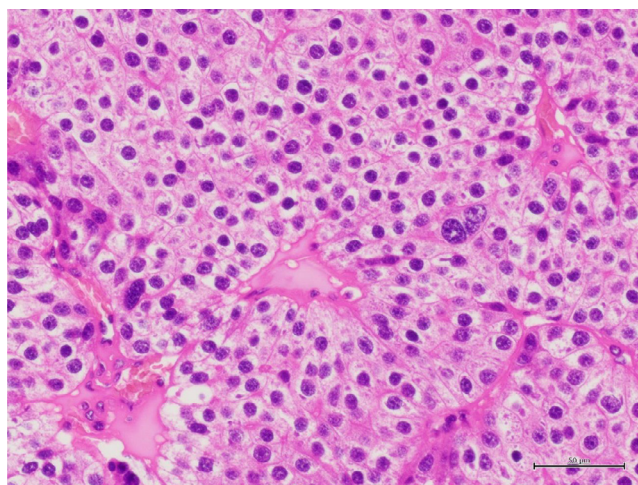


Fig. 8 – Parathyroid gland tissue at the initial surgery 8 years prior to Fig. 6. H&E Stain, magnification $\times 400$. No significant nuclear atypia is identified as in Fig. 6.

ever, MIBI is able to pass through membranes passively in response to negative mitochondrial membrane potentials and reversibly accumulates in the mitochondria [5]. Some studies have claimed that other lesions, such as primary lung cancers, also show accumulation of MIBI [6,7]. One study suggested that ^{99m}Tc -MIBI might be useful to differentiate between benign and malignant lesions for solitary pulmonary nodules [8,9]. In addition, ectopic parathyroid tumors are not usually encountered in the lung. For the reasons stated above, the pathological diagnosis of parathyroid adenoma for the previous and current samples stopped us from considering a metastatic lung lesion. In terms of the cr-assisted tomography findings, the nodule was solitary and relatively large. It also showed homogenous soft tissue density and a demarcated margin. Although it was nonspecific, it was also atypical for a primary lung or, to a lesser extent, metastatic cancer.

In conclusion, we report a case of recurrent primary hyperparathyroidism possibly caused by parathyroid adenocarcinoma metastasizing to the lung. It is difficult to distinguish between benign and malignant parathyroid tumors via pathological analyses alone. In addition to pathological findings, it is essential to integrate clinical status and imaging results when evaluating the malignant potential of tumors if a patient with hyperparathyroidism has tumors both inside and outside of the parathyroid gland.

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