Case Report
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대한영상의학회지

Multiorgan Involvements of Cowden Disease in a 50-Year-Old Woman: A Case Report and Literature Overview
50세 여자 환자에서 다기관을 침범한 Cowden병: 증례 보고 및 문헌고찰

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Cowden disease is the prototype of phosphate and, tensin homologue deleted on the chromosome 10 (*PTEN*) hamartoma tumor syndrome caused by germline mutations in the tumor suppressor *PTEN*, which is characterized by multiple developmentally disorganized benign growths, hamartomas, with an increased risk of both benign and malignant tumors. We present another case of Cowden disease in a 50-year-old woman. Besides the diagnostic criteria of Cowden disease, she had various manifestations in thyroid, lung, spleen, liver, pancreas, and muscle. As far as we know, it is the first case showing radiographic findings of hamartomatous lesions in thyroid, spleen, and pancreas, associated with Cowden disease.

Index terms
Multidetector Computed Tomography
Cowden Disease

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INTRODUCTION

Cowden disease (CD) is a rare multi-system disease characterized by various hamartomatous overgrowth of tissues from all three embryonic origins which increases risks for breast and thyroid cancers. Approximately 80% of patients with CD have an identifiable germline mutation in the tumor suppressor, phosphate and, tensin homologue deleted on the chromosome 10 (*PTEN*) gene (1, 2).

In this report, we present the various radiographical findings of multiple hamartomatous lesions involving multiple organs in one patient. In addition to classic findings, the patient was diagnosed with thyrolipoma, pancreas lipoma, and hepatic angiolipoma. To the best of our knowledge, these CT findings are introduced for the first time in this literature. This is followed by a review of clinical features, diagnostic criteria, and genetic conceptions of CD.

CASE REPORT

A 50-year-old woman visited our hospital for a postoperative follow-up evaluation after a modified radical mastectomy due to multicentric invasive ductal carcinoma of the right breast and right axillary metastatic lymphadenopathy (Fig. 1). She has a history of hyperthyroidism and takes medication for it. Her son has also been diagnosed with multinodular goiter.

She underwent CT scans of the chest and abdomen to determine metastasis. Chest CT scan showed multiple small non-calcified nodules, less than 5 mm, in both lungs periphery (Fig. 2A). Several small thin-walled air cysts were also seen in both lungs (Fig. 2B). The thyroid gland was diffusely enlarged with multiple hypodense nodules and macrocalcifications. Several thyroid nodules revealed fat attenuation areas (-120 Hounsfield units) (Fig. 3). On the abdomen CT, there were numerous hamartomatous lesions involving various organs. First, a 7.6 cm sized, well-defined, hypodense mass with a certain nodular enhancement pattern was seen in the right hepatic lobe, containing a few small fatty areas, which suggest angiolipoma (Fig. 4A). Other smaller hypodense nodules were also visible in the liver and spleen. There were several low-density cortical nodules in both kidneys, one of which had fat attenuation. Multiple small fatty

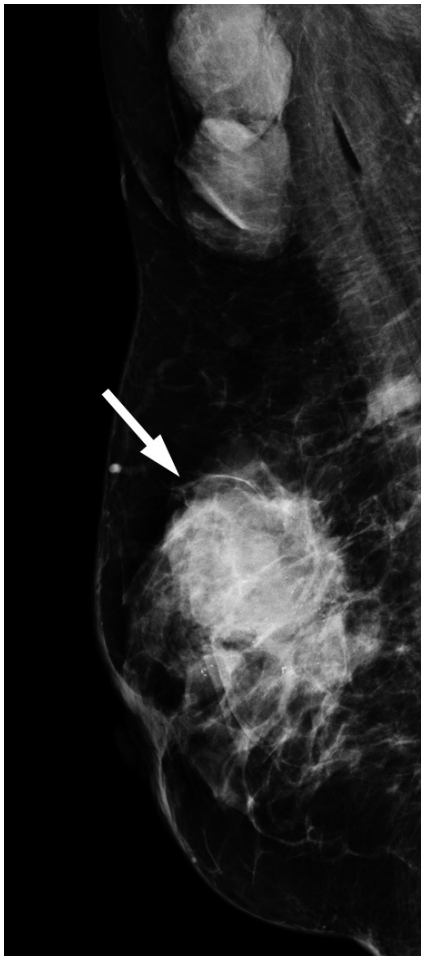
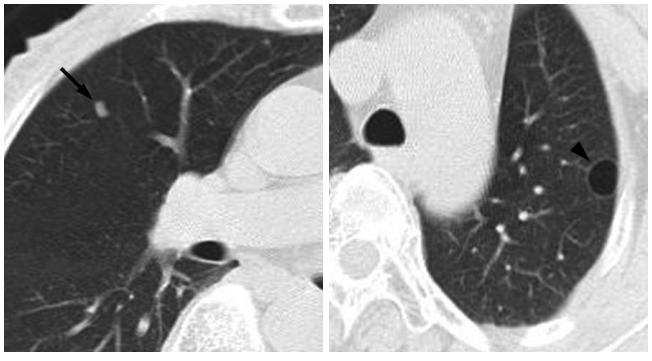


Fig. 1. Mammography shows a spiculated irregular mass with pleomorphic microcalcifications at the upper portion of the right central breast (arrow). Ipsilateral lymphadenopathy is associated.



A B

Fig. 2. Chest CT scans with mediastinal window setting.
A. A small discrete nodule is noted in the periphery of the lung (arrow). The nodule do not show FDG uptake on PET-CT scan (not shown). On the follow-up CT scan, there was no interval change of the nodule for 6 months (not shown).
B. A small lung cyst (arrowhead) is also seen with an unclear relation to CD, but it may be a component of the hamartomatous lesions.
Note.—CD = Cowden disease, FDG = fluorodeoxyglucose, PET-CT = positron emission tomography-CT

nodules were present in the pancreas (Fig. 4B). A small lipoma was suspected within the sigmoid colon (Fig. 4C). A fat containing enhanced nodule was also noted within the right gluteus muscle (Fig. 4D). Finally, a uterine myoma was detected. Fluorodeoxyglucose positron emission tomography-CT (FDG PET-CT), sequentially performed to rule out a possibility of metastasis, did not reveal an FGD uptake within the lesions detected on CT (Fig. 5). On ultrasonography of thyroid, the fat containing nodules on CT were echogenic, which represented thyrolipomas. Sequential fine-needle aspiration biopsy revealed a few follicular epithelial cells without evidences of malignancy. Sigmoidoscopy was performed and there were many small polyps along the rectosigmoid colon, which proved negative malignancy. However, we did not exclude the possibilities of hematogeneous metastasis of the lung from breast cancer because of the multiple small nodules on CT. We started systemic chemotherapy and breast irradiation. Next, follow-up CT scans of chest and abdomen, and PET/CT were checked every 6 months for 3 years. There were no changes in the lesions of body. The patient has remained alive with regular follow-up studies on breast cancer.

DISCUSSION

Cowden disease, a rare hereditary cancer syndrome, was first described in 1963 and named after the Cowden family, who was the first family documented with signs of the disease. The incidence of CD has been reported to be 1 in every 200000, although

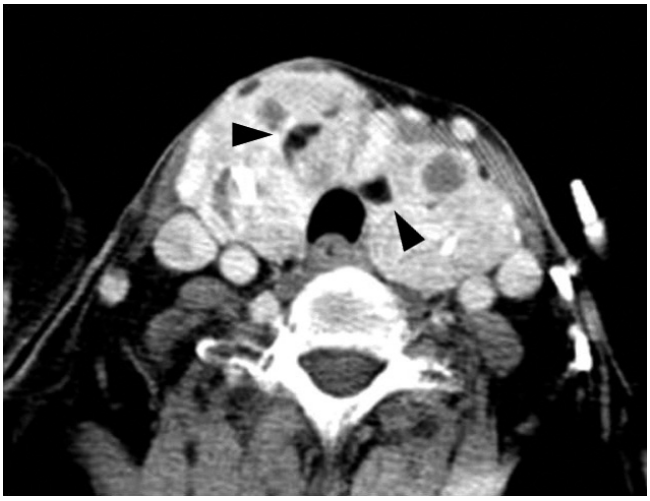


Fig. 3. CT scan shows diffuse enlargement of the thyroid gland with macrocalcifications. Note the multiple fat containing nodules (arrowheads), suggesting thyrolipomas.

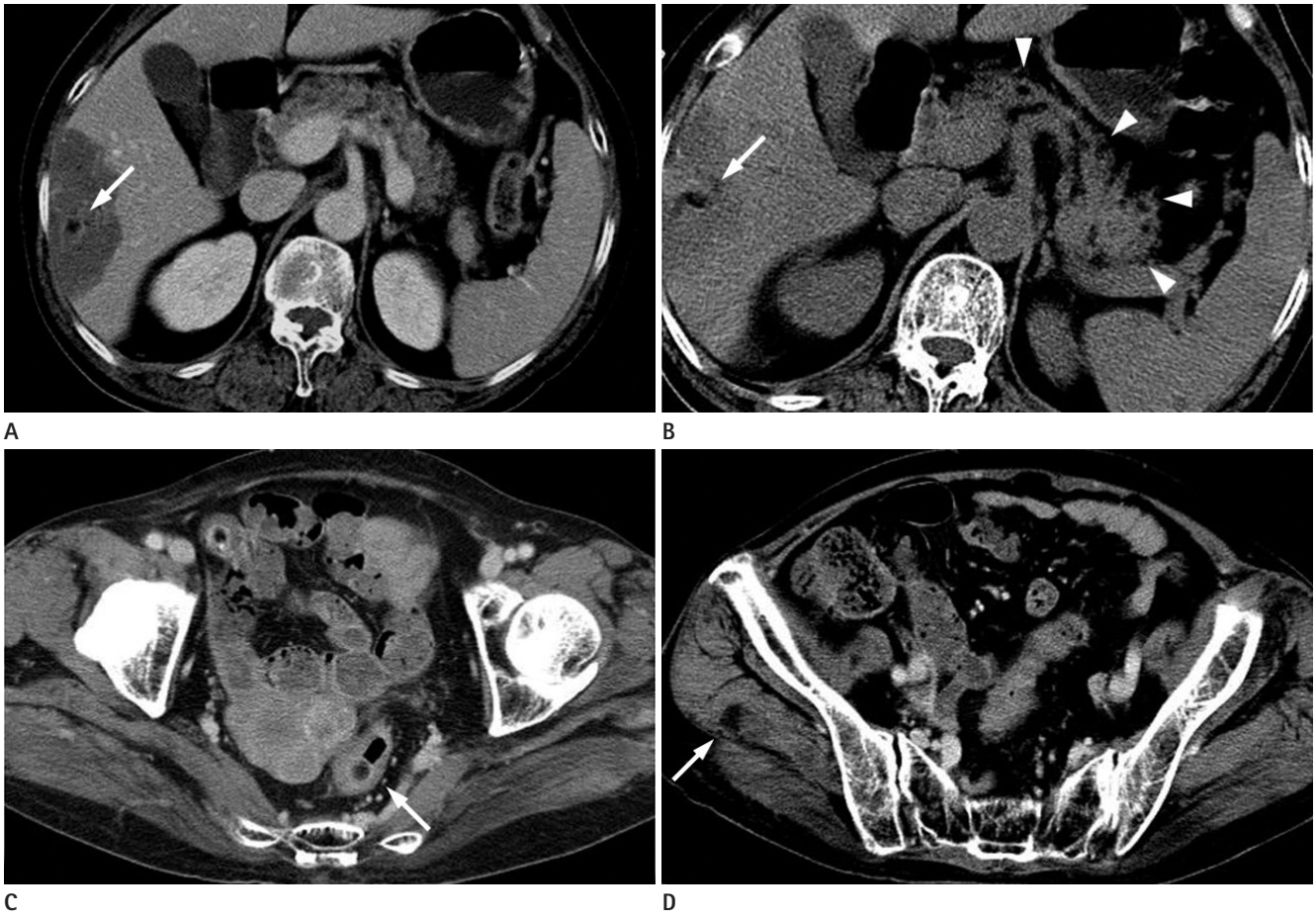


Fig. 4. Contrast enhanced CT scans of abdomen.
A. Hemangioma-like mass with fat density portion is seen in the right hepatic lobe (arrow).
B. Multiple tiny fat density nodules (arrowheads) noted in pancreas tail suggest lipomas. The aforementioned hepatic mass is also visible (arrow). The lesions are noted with no FDG uptake on PET-CT (not shown).
C. Low-density polyp is suspected within the sigmoid colon (arrow). The lesion is confirmed by colonoscopy.
D. Fat containing enhanced nodule is noted within the right gluteus muscle (arrow).
Note.—FDG = fluorodeoxyglucose, PET-CT = positron emission tomography-CT

this is likely underestimated due to the difficulties associated with making clinical diagnosis of the disease. It is considered as part of the *PTEN* hamartoma tumor syndrome (PHTS), which also includes Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, and Proteus-like syndrome, but CD is the only PHTS disorder associated with a documented predisposition to malignancies. The *PTEN* mutation frequency in individuals of CD has been estimated to be approximately 80% (3, 4).

Because of *PTEN* mutation, CD is characterized by multiple hamartomas of triploblastic origin, a high incidence of malignant tumors on the breast and/or thyroid gland, and an autosomal dominant pattern of inheritance. The characteristics of mucocutaneous lesions, such as trichilemmomas, papillomatous papules, and acral keratosis, are present in almost 100% of the

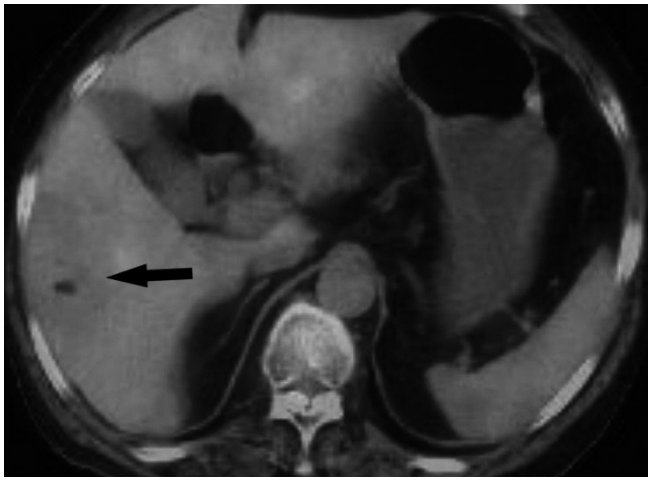


Fig. 5. PET-CT shows no FDG uptake in the hepatic lesion (arrow).
Note.—FDG = fluorodeoxyglucose, PET-CT = positron emission tomography-CT

cases; breast lesions are present in 76% of all cases, with carcinoma of breast occurring in 25-50% of female cases, and thyroid disease in 50-67% of all cases. Gastrointestinal polyps are found in 40% of the patients, and these are primarily found in the rectum and sigmoid. Breast cancer is the most frequent malignancy of CD, the thyroid, endometrium, and possibly other cancers are also prevalent. In women with CD, the lifetime risk of breast cancer is estimated to be 25-50%, compared to the general female population risk of approximately 12-13%. The lifetime risk of thyroid cancer has been estimated to 3-10% in CD patients (4, 5).

Table 1. Cowden Disease Testing Criteria

Individual from a family with a known *PTEN* mutation
Individual with a personal history of:
Bannayan-Riley-Ruvalcaba syndrome (BRR) or
Adult Lhermitte-Duclos disease (LDD) (cerebellar tumors) or
Autism spectrum disorder and macrocephaly or
Two or more biopsy proven trichilemmomas or
Two or more major criteria (one must be macrocephaly) or
Three major criteria, without macrocephaly or
One major and ≥ three minor criteria or
≥ Four minor criteria
At-risk individual with a relative with a clinical diagnosis of Cowden disease or BRR for whom testing has not been performed
The at-risk individual must have the following:
Any one major criterion or
Two minor criteria
Major criteria
Breast cancer
Mucocutaneous lesions
One biopsy proven trichilemmoma
Multiple palmoplantar keratoses
Multifocal or extensive oral mucosal papillomatosis
Multiple cutaneous facial papules (often verrucous)
Macular pigmentation of glans penis
Macrocephaly (megalocephaly) (i.e., ≥ 97th percentile, 58 cm in adult women, 60 cm in adult men)
Endometrial cancer
Non-medullary thyroid cancer
Multiple GI hamartomas or ganglioneuromas
Minor criteria
Other thyroid lesions [e.g., adenoma, nodule(s), goiter]
Mental retardation (i.e., IQ ≤ 75)
Autism spectrum disorder
Single gastrointestinal hamartoma or ganglioneuroma
Fibrocystic disease of the breast
Lipomas
Fibromas
Renal cell carcinoma
Uterine fibroids

Diagnostic criteria for CD were initially proposed by Salem and Steck in 1983, and later revised by consensus from the International Cowden Consortium of Researchers in 1996. It has been updated several times since and is now on the list of criteria included in the National Comprehensive Cancer Network Guidelines. Based on literature reports and expert consensus, the panel has recently revised both the lists of criteria associated with this genetic syndrome as well as the combinations of criteria which establishes that individuals are candidates for *PTEN* gene mutation testing (Table 1) (3).

For radiologists, CD is not a common disease entity to be diagnosed with imaging findings due to its rarity; it involves small, non-specific nodular lesions and minimal information is known about mucocutaneous lesions. The most common imaging finding in such patients was the presence of multiple, variably low-attenuated lesions on CT. These lesions are likely to represent a variety of mesenchymal tumors, most commonly the hamartomas, although some may have been lipomas or fibromas due to the histological confirmation that each lesion could not be performed. Therefore, for all patients, especially breast cancer patients with multiple unexplained soft tissue lesions throughout the body, this rare disease should be considered. This is because early detection of CD is critical to the early diagnosis of potential malignancies of various organs. In addition, genetic testing and screening of their family members should be recommended.

For our patient, multiple hamartomatous lesions involving multiorgans were revealed using various imaging modalities. In particular, fat-containing nodules involving the thyroid, pancreas, and liver were detected by CT scan and/or ultrasound examination. They showed characteristic findings of fat density on CT and heterogeneous hyperechogenicity. As far as we know, this is the first CT finding of thyrolipoma in CD. Thyroid pathology findings were reported in the CD patient as follows: multiple adenomatous nodule in a background of lymphocytic thyroiditis, papillary carcinoma, follicular carcinoma, C-cell hyperplasia, and follicular adenoma (6). In addition, there has not been a report on CT patient with pancreas lipoma and hepatic angiolipoma. We propose that these lesions, although rare, are the components of hamartomatous lesions. None of the small neoplastic lesions showed any FDG uptakes on the PET-CT scan. Follow-up imaging studies (chest and abdominal CT and PET-CT dur-

ing 3 years) did not reveal any interval changes in the sizes and configurations of multiple hamartomatous lesions.

In summary, our patient demonstrated a much wider spectrum of imaging findings, including breast cancer, thyrolipoma, hepatic angioma, and pancreas lipoma. Detection of multiple hamartomatous lesions of different characteristics in a patient with other local and systemic pathologies prompts further evaluations for CD. Diagnosis of CD is crucial, since it can lead to a surveillance of cancers and increase the expected life span of the patient and their family members.

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50세 여자 환자에서 다기관을 침범한 Cowden병: 증례 보고 및 문헌고찰

이은재 · 정원상 · 고정민 · 박현진

Cowden병은 종양억제인자 phosphate and, tensin homologue deleted on the chromosome 10 (*PTEN*)의 유전자변이에 기원하는 *PTEN* 과오종증후군의 원형으로, 과오종의 다발성 발생을 특징으로 하며 양성 종양뿐만 아니라 악성종양의 위험이 높은 질환이다. 저자들은 50세 유방암 환자에서 갑상선, 폐, 비장, 간, 췌장 그리고 근육을 포함한 다양한 장기에 과오종을 보였던 Cowden병을 경험하였고, 특히 갑상선과 비장 그리고 췌장을 침범하는 Cowden병의 영상소견은 아직 보고된 바가 없어 보고하고자 한다.

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